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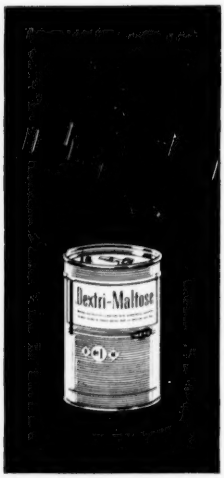

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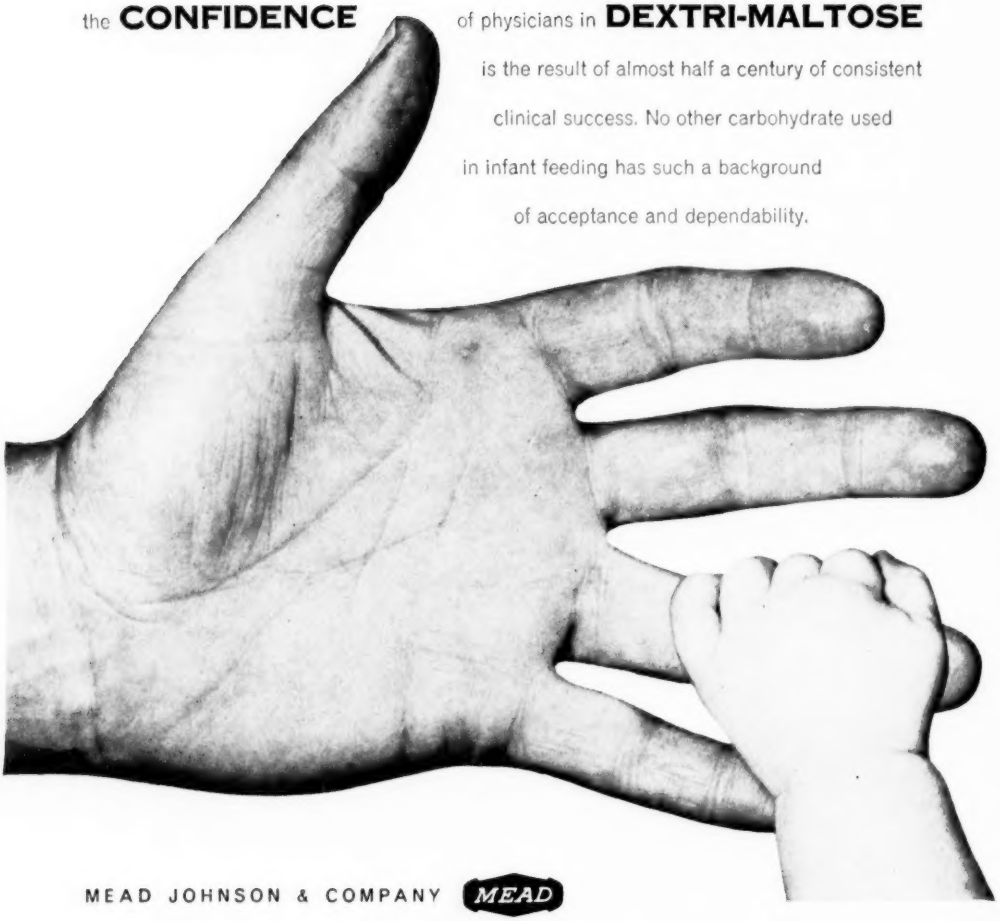

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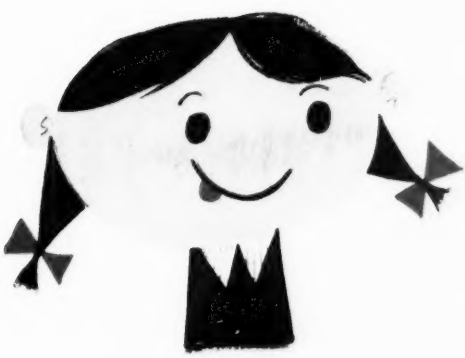

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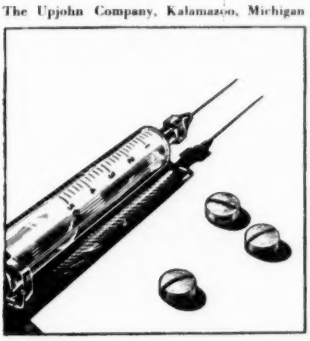

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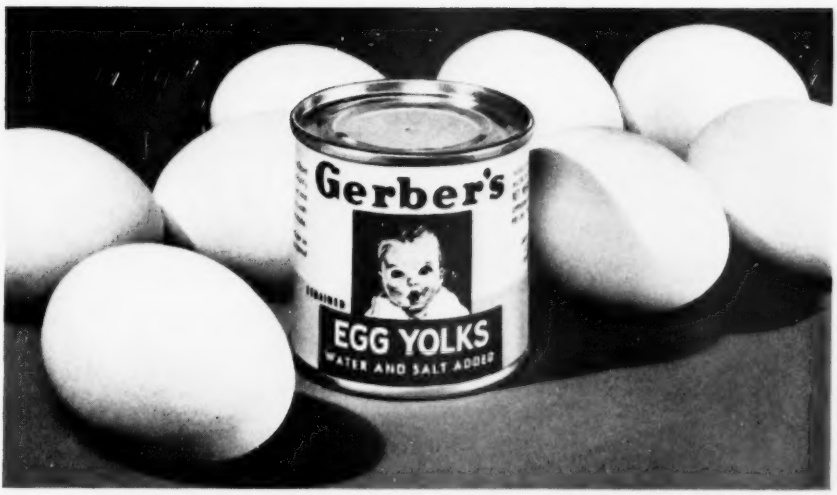

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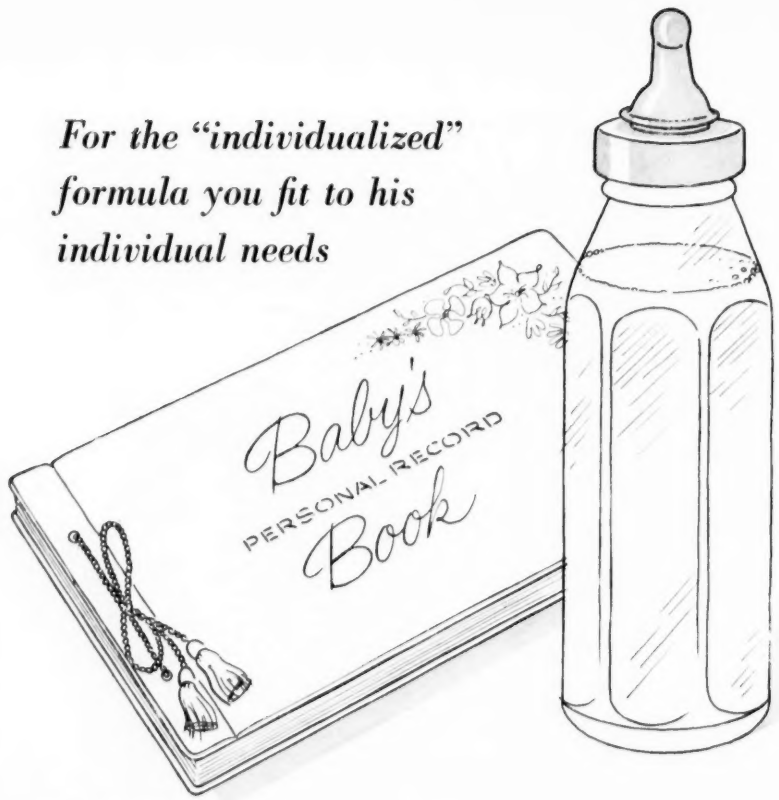

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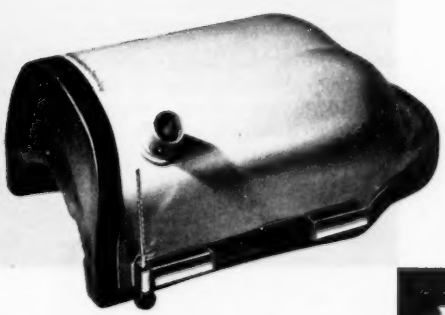

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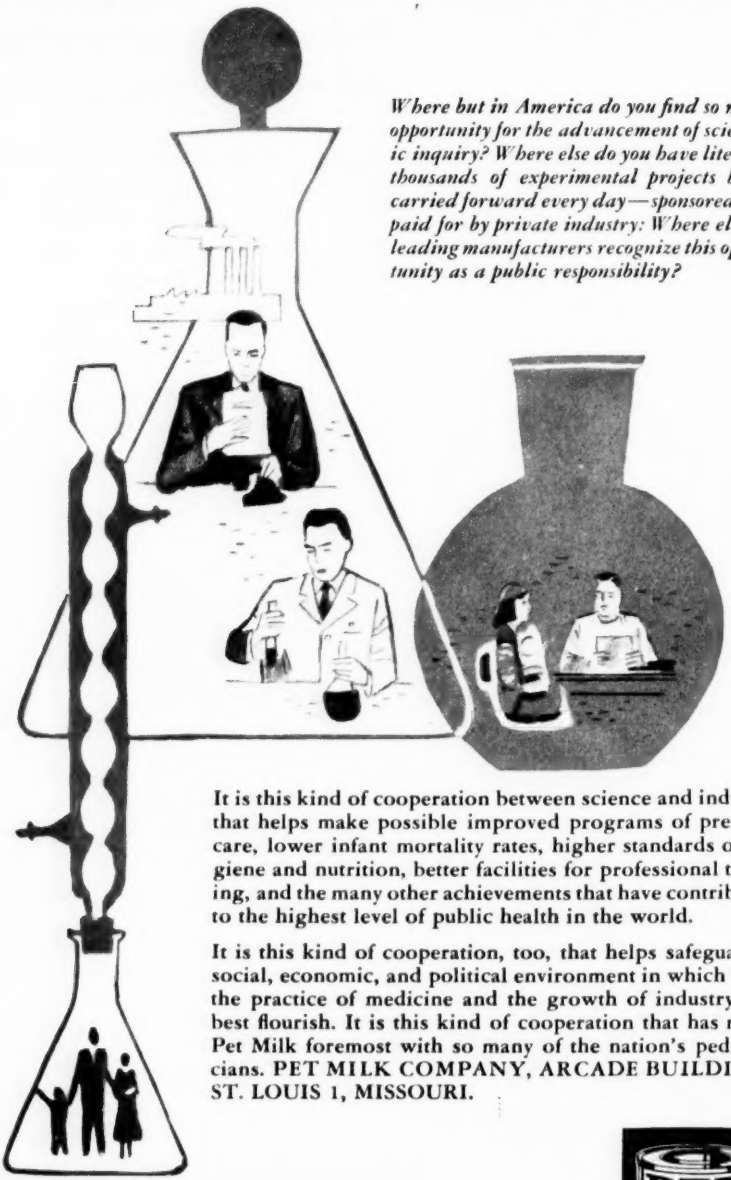

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STUDIES IN RESPIRATORY INSUFFICIENCY

I. Carbon Dioxide and Oxygen Studies in Early Respiratory Paralysis in Poliomyelitis

DAVID G. DICKINSON, M.D.
JAMES L. WILSON, M.D.
AND
BRUCE D. GRAHAM, M.D.
ANN ARBOR, MICH.

IN THE last few years, because of availability of artificial aids to respiration, a great deal of attention has been given to the early detection of insufficiency of respiration, particularly in the narrow field of respiratory involvement in poliomyelitis.[1]

There exist considerable differences of opinion as to the proper time at which a patient with early respiratory muscle paralysis in poliomyelitis should be given artificial aid. It has been argued that the early use of a respirator increases the risk of addiction to the respirator and the chance of the patient's developing an excessive pulmonary ventilation, on which he becomes dependent because of the early use and its excessive use. On the other hand, many believe that the early use of the respirator, if it succeeds in giving rest, is of advantage.[2]

It has been our hope to develop laboratory techniques which would detect early respiratory insufficiency before definite clinical evidence was obtained in cases in which it is necessary to give respiratory aid early.

The present article consists of a report and analysis of biochemical data collected on patients with acute poliomyelitis to demonstrate as early as possible in the disease indices of oxygen lack or carbon-dioxide retention resulting from respiratory insufficiency.

A following article will describe the clinical signs of early respiratory difficulty.

A series of patients with acute poliomyelitis were studied, some of whom did not show evidence of respiratory muscle paralysis, some of whom did when first seen, and in some of whom respiratory insufficiency developed later.

From the Poliomyelitis Respirator Center, Department of Pediatrics, University of Michigan Medical School.

The Poliomyelitis Respirator Center is supported by a grant from the National Foundation for Infantile Paralysis, Inc.

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2. Conference on Respiratory Problems in Poliomyelitis, Sponsored by the National Foundation for Infantile Paralysis, Houston, Texas, Jan. 26-28, 1951.

CLINICAL MATERIAL

Data were collected on 35 patients with acute poliomyelitis ranging from 6 weeks to 42 years of age. All were in the first week of their disease. None of these patients had clinical evidence of airway obstruction from bulbar involvement or other cause, and all but two were felt to be free of intrapulmonary disease. The two exceptions are indicated in the data and discussed. The patients fell logically into two groups.

Group 1.—Group 1 includes those patients upon whom chemical and clinical appraisal was made, but in whom respiratory paralysis did not develop subsequently.

Group 2.—Group 2 includes those patients in whom respiratory paralysis of sufficient severity to necessitate the use of a respirator developed. This group must be further broken down into three subgroups.

Group 2A.—Subgroup A includes those who entered the hospital early in the course of their disease, before respiratory involvement could be suspected on any clinical grounds, and upon whom serial observations were made up to and including the time when mechanical-respirator aid became necessary.

Group 2B.—Subgroup B includes those patients upon whom observations were made at the time mechanical respirator aid appeared indicated on clinical grounds.

Group 2C.—Subgroup C includes those patients sent in by ambulance, often from distant points, because they were considered by their local physicians to present respiratory emergencies. All of this group were placed in respirators soon after arrival but not until clinical evaluation and sampling had been completed.

SAMPLING PROCEDURE

Five milliliters of arterial blood was obtained from the femoral artery by direct puncture after local infiltration of procaine.

The 5 ml. syringes were previously prepared by filling with 5 ml. of heparin (40 mg. per 100 ml. of solution) and dried in vacuo. A drop of heparin solution was placed on the tip of the plunger, which was also dried in vacuo. The plunger of the syringe was coated with light mineral oil U. S. P. After arterial puncture, any small bubble of trapped air was expelled, and the needle was then replaced with a serum bottle rubber cap. The syringe was rotated to insure mixing with the anticoagulant and then packed in ice for immediate analysis.

LABORATORY METHODS

Analyses were usually performed in duplicate. Blood pH was determined with use of the Cambridge Electron-Ray pH Meter (research model).[3] The meter was kept in an incubator (Liedberg Anhydric Incubator), which was maintained at a temperature of 38 C. All determinations were performed at this temperature. The blood sample was ejected directly from the sample syringe into a microcondenser type glass electrode. Seven minutes were allowed for temperature equilibration. Four readings were taken. The meter was calibrated before each sample and checked again afterward with pH standard solution prepared from Coleman buffer tablets (pH 7.40 + or — 0.02 at 30 C.). Duplicate determinations were made on each sample.

Total plasma CO_2 content was determined on 0.2 ml. of plasma by the manometric method of Van Slyke[4] and Neill.

The CO_2 tension of the plasma (pCO_2) was calculated by the Lyon chart for graphic calculation of serum or plasma values by the CO_2 solubility equation and the Henderson-Hasselbalch equation.[5]

3. Obtainable from Cambridge Instrument Co., Ossining, N. Y.

4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, Vol. 2.

5. Peters and Van Slyke,[4] p. 883.

All pulmonary air movement studies were carried out with a Sanborn horizontal bellows metabolism machine.[6] The machine was calibrated by introducing known amounts of air and the length of tracing measured, after which the air displacement per centimeter of pen displacement was calculated.

RESULTS

Group 1.—In this group there was no respiratory muscle paralysis. Measurements were made on 15 patients in whom at no time clinically recognizable respiratory muscle weakness developed.

The arterial pH was elevated above normal in 11 patients and was normal in 4. The average pH for this group was 7.49, with a range from 7.40 to 7.65.

The total CO_2 content varied from 18.9 mEq. to 26.8 mEq. per liter, with an average value of 23.1 mEq. per liter.

TABLE 1.—*Biochemical Measurements for Patients in Whom No Recognizable Respiratory Muscle Paralysis Developed (Group 1)*

Patient	Age, Yr.	Sex	Day of Disease	pH	CO_2 Content, mEq./L.	CO_2 Tension, Mm. Hg	Oxygen Saturation, %	Clinical Notes
But	16	M	2	7.51	21.8	26	95	
Dav	7	F	7	7.49	23.1	30	100	Patient and mother terrified
Der	18	F	3	7.42	24.2	37	97	
Eng	17	F	4	7.65	18.9	17	..	Tetany
Sex	16	M	2	7.40	25.5	39	..	
Kin	18	F	3	7.44	23.8	34	..	
Mil	21	F	3	7.50	22.4	28	97	
New	16	F	4	7.52	19.5	30	96	Paralysis left leg; terrified
Paw	18	M	3	7.42	26.8	40	..	
Ray	3	F	1	7.51	22.8	28	96	Left facial paralysis; terrified
Sou	21	F	4	7.48	24.0	32	..	
Wit	17	F	5	7.53	25.4	31	96	
Gag	23	F	4	7.53	25.6	30	96	
Wei	22	F	5	7.51	22.4	27	92	7½ mo. pregnant
Van	15	M	4	7.50	20.8	26	..	
Average for group				7.49	23.1	30	96	
Range for group				7.40-7.65	18.9-26.8	17-40	92-100	

The calculated arterial CO_2 tension was less than normal in 13 of the 15 patients and normal in the remaining 2, with a range from 17 to 40 mm. Hg and an average of 30 mm. Hg.

Arterial hemoglobin oxygen saturation was determined for 9 of the 15 patients in this group. All but one of these determinations were within the normal range. The average for the group was 96%. The lowest determination was 92% and the highest 100%.

Results for this group are summarized in Table 1.

Group 2.1.—Four patients were studied before respiratory muscle paralysis became apparent and again at the time that mechanical respiratory assistance was deemed advisable on clinical grounds.

One patient (Sel) was so uncooperative in accepting respirator aid that she afforded an opportunity to study her for 24 hours after a mechanical respirator appeared clinically indicated. The data are included in the table but omitted from the averages, since the clinical situation is outside the specifications for the group.

6. Available from Sanborn Co., Cambridge, Mass.

Prior to the onset of paralysis, each of these four patients had either an elevated pH or a decreased CO_2 content, or both, with a resultant low CO_2 tension. As paralysis progressed to the point where a respirator seemed necessary, the pH did not change significantly in three patients (Moh, Sch, and Sel). The CO_2 content remained unchanged in two of these three and increased from 19 to 24 mEq. per liter in the third (Sel).

Although the CO_2 tension increased moderately in patient Sel, it remained considerably below the normal level in all three of these patients.

In the fourth patient (Tol) there was a moderate decrease in pH, increase in CO_2 content, and a shift of CO_2 tension from a low to a high level during the period when respiratory muscle paralysis was developing.

TABLE 2.—*Patients Studied Before Respiratory Muscle Paralysis and Again Just Prior to Receiving Artificial Respiratory Aid (Group 2A)*

Patient	Age, Yr.	Sex	Day of Disease	Vital Cap.	Min. Vol.	pH	CO_2 Content, mEq./L.	CO_2 Tension, Mm. Hg	O_2 Sat., %	Clinical Notes
Moh	28	F	5	.....	.....	7.47	27.3	37	83	Has pneumonia but no respiratory muscle paralysis
			6	.....	.....	7.49	27.5	35	88	Clinically needs respirator
Sch	28	F	2	.....	.....	7.43	21.4	27	100	No. resp. muscle paralysis
			3	.....	.....	7.40	21.7	30	95	Clinically needs respirator
Sel	16	F	4	2,070	11,836	7.50	19.0	24	93	No. resp. muscle paralysis
			5	683	9,984	7.50	22.0	29	..	
			6	434	8,680	7.50	24.0	30	..	Clinically needs respirator
			7	?	.....	7.26	31.0	65	91	Completely exhausted
Tol	16	M	3	3,519	.....	7.40	22.0	35	100	No. resp. muscle paralysis
			5	600	.....	7.34	26.6	45	100	Clinically needs respirator

	Average		Range	
	Before Paralysis	After Paralysis	Before Paralysis	After Paralysis
pH	7.45	7.43	7.40- 7.50	7.34- 7.50
CO_2 Cont.	22.4	24.9	19.0 -27.3	21.7 -27.5
pCO_2	31.0	35.0	24.0 -37.0	30.0 -45.0
O_2 Sat.	94%	98.5%	83.0 -100%	88.0 -100%

In two patients of this group, arterial oxygen saturation was significantly reduced before the onset of respiratory paralysis. One of these had frank clinical pneumonia. The other had severe bulbar involvement and was extremely toxic but had no specific signs of abnormality of the lungs. It is important to note, however, that in none of the four patients did arterial oxygen saturation change significantly during the period of progressive respiratory paralysis.

The data concerning this group are summarized in Table 2.

Group 2B.—There were 10 patients in Group 2B. This is the group upon whom a single set of observations was made at the time mechanical respiratory assistance appeared to be clinically indicated.

The pH was elevated in seven and normal in three, with a range from 7.43 to 7.53 and an average of 7.48.

The CO_2 content varied from 23.3 to 28.8 mEq. per liter, with an average of 25.9 mEq. per liter.

The CO_2 tension was significantly low in 7 of the 10 patients and normal in the remaining 3, with a range from 30 mm. Hg to 40 mm. Hg and an average value of 35 mm. Hg.

The arterial oxygen saturation was determined on seven patients. It varied from 93% to 100%, with an average of 96%.

The data concerning this group are summarized in Table 3.

Group 2C.—This is the group of six patients who were transferred from other cities after their attending physicians had decided that a mechanical respirator was needed. All patients were transported by ambulance over distances of 30 to 75 miles

TABLE 3.—*Patients Studied Just Prior to the Institution of Artificial Respiratory Aid (Group 2B)*

Patient	Age	Sex	Day of Disease	Vital Cap.	Min. Vol.	pH	CO_2 Content, mEq./L.	CO_2 Tension, Mm. Hg	O_2 Sat., %
Atw	25 yr.	F	3	727	9,980	7.49	23.3	30	95 (est.)
Cls	19 yr.	M	3	742	6,776	7.45	28.8	40	95
Gei	24 yr.	F	4	...	.....	7.48	24.0	33	97
Lov	8 yr.	..	3	...	.....	7.47	26.5	36	100
Sny	6 wk.	M	7	...	.....	7.48	27.5	36	92.5
Ste	33 yr.	F	2	802	8,172	7.49	23.7	31	..
Dob	4 yr.	M	6	...	.....	7.43	27.4	40	96
Mac	16 yr.	F	8	788	9,534	7.52	25.7	31	..
Ver	22 yr.	M	3	1,080	.....	7.53	26.5	31	94
Mor	3 yr.	F	4	...	.....	7.43	25.8	38	97
Average for the group						7.48	25.9	35	96
Range for the group						7.43-7.53	23.3-28.8	30-40	93-100

TABLE 4.—*Patients Transported from Other Cities Without Artificial Respiration After the Need for Mechanical Respiratory Aid Became Apparent (Group 2C)*

Patient	Age, Yr.	Sex	Day of Disease	Vital Cap.	Min. Vol.	pH	CO_2 Content, mEq./L.	CO_2 Tension, Mm. Hg	Sat., %	Clinical Notes
Coo	24	F	4	970	.....	7.50	23.0	29	95	
Gas	24	F	4	970	.....	7.56	28.4	31	96	Exhausted; O_2 given during transport
Vre	20	F	3	375	.....	7.40	27.2	44	91	Exhausted; O_2 given during transport
Morr	25	M	4	300	7,700	7.40	30.4	47	84	
Dot	31	M	4	620	.....	7.52	23.9	29	90	O_2 given during transport
Lyk	7	F	4	242	4,706	7.45	25.8	36	..	(Venous sample)
Average for the group						7.47	26.4	36	93	
Range for the group						7.40-7.56	23.0-30.4	29-47	84-99	

(48 to 120 kilometers). Some were given oxygen by mask en route, as indicated in Table 4. None were given artificial respiration of any type. None were receiving oxygen at the time of sampling.

It will be noted that all vital-capacity measurements were extremely low, varying from 242 cc. to 970 cc., with an average of 580 cc.

The pH was elevated in three patients and normal in three, with a range of 7.40 to 7.56 and an average value of 7.47.

The total CO_2 content was slightly low in two patients, normal in one patient, and slightly elevated in three patients, with a range of 23 to 30.4 mEq. per liter and an average of 26.4 mEq. per liter.

The CO_2 tension was slightly elevated in two patients and low in the remaining four, with an average of 36 mm. Hg and a range from 29 to 47 mm. Hg.

Oxygen saturation was determined for five patients; it was low in the two patients with elevated CO_2 tension and normal in the remaining three.

Data for this group are summarized in Table 4.

It has been emphasized that biochemical measurements were made on all patients requiring a respirator just prior to the time such mechanical breathing assistance was instituted. These include the final set of measurements for each patient in Group 2A as recorded in Table 2 and all measurements of Groups 2B and 2C as recorded in Tables 3 and 4.

COMMENT

Pulmonary ventilation is one of the most precisely regulated activities of the body. It is generally agreed that this degree of precision is necessary for the regulation of carbon dioxide. Bodily requirements for ventilation are determined primarily by metabolic production of CO_2 and by the relationships of blood bicarbonate, CO_2, and pH.[7] When CO_2 production is elevated by increase in metabolism, ventilation normally increases and the arterial CO_2 tension remains within 1 or 2 mm. of 40 mm. Hg. A deviation of only a few millimeters above this value constitutes respiratory acidosis, and a deviation in the other direction, respiratory alkalosis.

Arterial oxygen tension is, of course, also affected by pulmonary ventilation, and, conversely, it constitutes one of the chemical mechanisms controlling ventilation.[7b] However, because of the characteristics of the hemoglobin oxygen dissociation curve, fairly large fluctuations of ventilation may occur without reflecting corresponding changes in oxygen saturation. It will be recalled that the top portion of the hemoglobin oxygen dissociation curve is relatively flat and that the alveolar oxygen tension is decreased to 50% of normal before hemoglobin saturation drops to 85%, which is about the level where cyanosis generally becomes clinically apparent.[8] In other words, underventilation or respiratory failure must have progressed to a marked degree before one could expect cyanosis to appear as a clinical sign of such failure. Obviously, then, cyanosis is a poor clinical sign upon which to depend when deciding when a respirator should be used. Determination of arterial oxygen saturation would be somewhat better, since significant drops that are not clinically apparent can be measured.

Blood pH or plasma CO_2 content might be helpful each by itself, except that many factors not related to breathing, such as dehydration and ketosis, can affect one or the other of these, making interpretation of results exceedingly difficult.

The CO_2 tension, on the other hand, is essentially a function of pulmonary ventilation and its adjustments to body requirements. Therefore, one might expect the CO_2 tension to be the most sensitive laboratory indication of physiologic respiratory failure.

If the foregoing concepts are kept in mind, analysis of the data presented affords several interesting deductions regarding behavior of the respiratory system in acute poliomyelitis.

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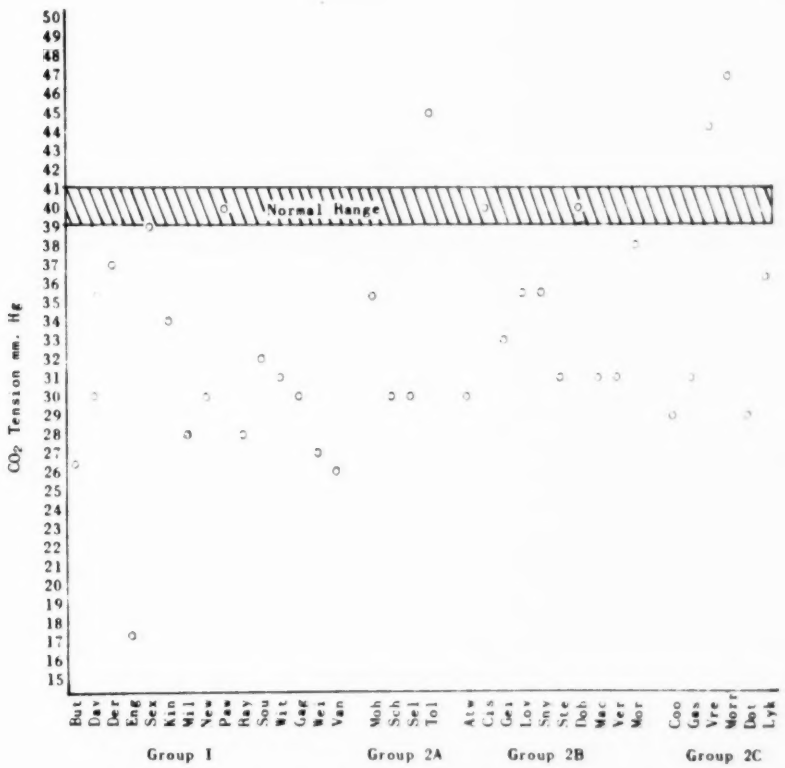
7. (*a*) Haldane, J. S., and Priestley, J. G.: The Regulation of Lung Ventilation, J. Physiol. **32**:224-266, 1905. (*b*) Campbell, J. M. H.; Douglas, C. G.; Haldane, J. S., and Hobson, F. G.: The Response of the Respiratory Center to Carbonic Acid, Oxygen and Hydrogen Ion Concentration, J. Physiol. **46**:301-318, 1913.

8. Geraci, J. E., and Wood, E. H.: The Relationship of the Arterial Oxygen Saturation to Cyanosis, M. Clin. North America **35**:1185-1202 (July) 1951.

First, we were somewhat surprised to learn that of the 15 patients without respiratory muscle paralysis (Group 1), 13 were hyperventilating and were in respiratory alkalosis. The average CO_2 tension of 30 mm. Hg for this group is quite definitely below the normal range and represents a significant shift. The four patients in Group 2A were also in respiratory alkalosis prior to the onset of their paralysis. It is our belief that this consistent pattern of overbreathing is the result of apprehension or fear, which is probably present in most patients with acute poliomyelitis.



Comparison of the arterial CO_2 tension of all patients in the study.

Accepting the fact that most patients with acute poliomyelitis are in a state of respiratory alkalosis early in their disease, it is important to compare this situation with that of the patient who clinically needs a respirator. Turning our attention to groups 2A and 2B, we find that of these 14 patients with obvious dyspnea due to paralysis 10 were still in a state of respiratory alkalosis as indicated by a reduced CO_2 tension and 3 of the remaining 4 appeared still able to maintain normal pulmonary ventilation. Only one (Tol) was in a state of mild respiratory failure, as evidenced by CO_2 retention, so mild that his oxygen saturation still remained normal. Even of the six patients who were left without respiratory aid for considerably longer than is usually considered desirable (Group 2C), only two were in respiratory acidosis.

The CO_2 tensions of all patients included in the study are recorded graphically in the Chart, which serves to illustrate the exceedingly high incidence of respiratory alkalosis.

We must conclude, then, that in the majority of poliomyelitis patients with progressive respiratory paralysis, clinical signs of dyspnea will develop before there is actual failure of the respiratory mechanism to provide adequate ventilation.

Since our laboratory procedures, except those determining vital capacity, are designed to measure respiratory failure, one cannot expect them to replace sound clinical observation and good judgment in determining when a mechanical respirator should be used. It is evident that with an unobstructed airway and freedom from intrapulmonary disease, a poliomyelitis patient will give adequate clinical warning of his need for a respirator before he suffers from anoxia or CO_2 retention.

The data reported here showing the high incidence of respiratory alkalosis in patients before they are placed in the respirator has a direct bearing upon the problem of "respirator addiction." It has been previously reported and mentioned in this paper that patients in a respirator often seem to be dependent upon a degree of pulmonary ventilation considerably greater than they need in health and become adjusted to a state of alkalosis which is abnormal. However, it can be seen that it is not necessary that the respirator itself bring this about, since it occurs before the use of the respirator is initiated. Further study of this situation is indicated and will be presented in a later paper.

SUMMARY

Concomitant laboratory studies and clinical observations were made on a group of 35 poliomyelitis patients in the first week of their disease in an attempt to determine whether or not laboratory evidence of respiratory insufficiency preceded clinical dyspnea in those in whom respiratory muscle paralysis developed.

Observations were made on 15 patients who at no time had detectable involvement of the respiratory muscles. These patients were uniformly found to be in a state of respiratory alkalosis, presumably from fear or apprehension.

Twenty patients were studied at the time mechanical respiratory assistance appeared clinically indicated. Fourteen of these were still hyperventilating and in a state of respiratory alkalosis at the time that respirator aid was instituted.

CONCLUSIONS

1. Most patients with acute poliomyelitis are in a state of respiratory alkalosis early in their disease.

2. Those patients in whom respiratory muscle paralysis develops continue in a state of respiratory alkalosis for a considerable period after clinical signs of dyspnea appear.

3. The clinical picture usually associated with the need for artificial respiration in poliomyelitis is that of decreased respiratory reserve, or increased effort, and is usually not accompanied by actual respiratory failure until after the clinical picture of dyspnea has become well established. Therefore, given a normal airway and freedom from intrapulmonary disease, the average poliomyelitis patient will give ample warning of his need for a respirator before anoxia or CO_2 retention occurs.

4. Although extremely valuable for adjunct aid and for guiding later care of respirator patients, laboratory tests cannot replace careful clinical observations as criteria for deciding when a mechanical respirator should first be used.

AEROSOL TRYPSIN IN RESPIRATORY COMPLICATIONS OF BULBAR POLIOMYELITIS

Report of a Case

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ONE OF the many difficulties encountered in the management of bulbar poliomyelitis has been the development of respiratory distress resulting from accumulation and inspissation of mucus within the respiratory tract with resultant segmental or even massive atelectasis. Until recently, the most effective methods for prevention and correction of such disturbing complications included postural drainage, frequent suctionings, and occasional use of aerosol solutions to supply moisture and prevent infections. Added to this was the more complex procedure of bronchoscopic aspiration. Unfortunately, the first three methods mentioned have not always or generally proved reliable, whereas the last method required specialized experience and technique. Many small community hospitals are not sufficiently staffed or equipped to offer the more complex method, even though it is generally more desirable and effective.

It is the purpose of this preliminary report to describe another method which can be adapted to even the smallest hospital and which can be relied upon to be reasonably effective.

Recent studies [1] have indicated the effectiveness of aerosol enzymatic digests in the resolution of bronchopulmonary exudates. It was felt that a trial of similar therapy was warranted in the management of a case of bulbospinal poliomyelitis.

REPORT OF CASE

E. P., a 6-year-old white boy, was admitted to the Memorial Hospital of Sheridan County to the service of Dr. James Wild on Oct. 6, 1952, with the diagnosis of high spinal poliomyelitis. Three days after admission bulbar signs developed in the patient, with extreme respiratory difficulty associated with excessive nasopharyngeal mucus requiring emergency tracheotomy. Frequent suctioning through the tracheotomy tube was necessary to maintain a patent airway.

From the Memorial Hospital of Sheridan County, Wyoming.

1.(*a*) Limber, C. R., and others: Enzymatic Lysis of Respiratory Secretions by Aerosol trypsin, J. A. M. A. **149**:816-821 (June 28) 1952. (*b*) Steigman, A. J., and Scott, C. H.: Trypsin in Poliomyelitis Patients with Tracheotomy, ibid. **150**:1403-1404 (Dec. 6) 1952. (*c*) Miller, J. M., and others: Interbronchial Uses of Streptokinase and Streptodornase in the Treatment of Slowly Resolving Pneumonias, Dis. Chest. **23**:149-153 (Feb.) 1953. (*d*) Craven, J. F.: Treatment of Obstructive Atelectasis by Aerosol Administration of Proteolytic Enzymes, J. Pediat. **42**:228-230 (Feb.) 1953.

Intermittent positive-pressure oxygen[2] and antibiotic aerosol therapy was administered several times daily. In spite of such therapy, extremely tenacious mucus accumulated which often made it difficult to suction the tracheotomy tube and the trachea. In view of the increasing difficulties, gradual deterioration of the patient, and previous unfortunate experiences with atelectasis in poliomyelitis, aerosol trypsin (Tryptar, the Armour Laboratories) therapy was instituted. The recommendations for dosage were adapted from Limber.[1a] Fifty thousand Armour units (50 mg.) of Tryptar were dissolved in approximately 1 cc. of Tryptar Diluent (Sorensen's Phosphate Buffer Solution, pH 7.1). This amount was aerosolized through the intermittent positive-pressure apparatus twice a day with an oxygen flow of 6 to 8 liters per minute. Ten minutes before each aerosol trypsin administration the child was given 10 mg. of diphenhydramine (Benadryl) hydrochloride intramuscularly to prevent possible allergic reactions. Usually, the therapy was completed in about 10 or 15 minutes. There was general improvement in the patient following each such administration, with a marked increase in the fluidity of the aspirated secretions, making aspirations much easier and more effective. The therapy with aerosol was continued twice daily for seven days. With the gradual improvement of the patient, aerosol trypsin therapy was given only once daily for four more days and then discontinued. There was a gradual but progressive increase in tidal volume. Subsequently, several respiratory infections developed in the patient, and at one time segmental atelectasis was demonstrated by x-ray and by a definite decrease in tidal volume. Therapy with antibiotics, which had been in progress continuously, was made more effective with higher dosages, and aerosol trypsin therapy was reinstituted. It was given twice daily for four days. There was prompt improvement, with apparent clearing of the atelectasis, as shown by x-ray. No ill effects were noted either during or immediately following aerosol trypsin therapy, even though numerous aerosols were administered to this patient.

COMMENT

One of the most common causes of fatality in respiratory complications in acute bulbar poliomyelitis is the development of mucous plugs and atelectasis with superimposed pneumonia. Management of such complications has been shown to be effective in other diseases through the use of aerosol enzymatic digests. Its apparent effectiveness in a case of bulbar poliomyelitis is indicated by the case presented.

SUMMARY AND CONCLUSIONS

In view of the present seasonal increase in poliomyelitis, attention is directed through a case report to the apparent effectiveness of aerosol trypsin therapy in the management of respiratory complications encountered in bulbar poliomyelitis. It is felt that this method of therapy merits further trial and study.

Permanente Clinic, 2606 N. E. Broadway (Dr. Varga).

2. A Bennett Flow Sensitive Pressure Breathing Therapy Unit was used for this purpose.

TRANSABDOMINAL PNEUMOPERITONEUM AS AN AID IN THE DIAGNOSIS OF SEX-ENDOCRINE DISTURBANCES

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AND
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ANY SIMPLE technical procedure is of value when it aids in establishing a clinical diagnosis without the necessity of an exploratory operation. It is our aim to show how pneumoperitoneum can be adapted to children for this purpose in various sex-endocrine disturbances. To the best of our knowledge, such a procedure has not been described in pediatric literature, and no mention is made of its use in children in gynecological writings and texts.

From a historical standpoint, diagnostic pneumoperitoneum is not new. Alvarez [1] first introduced the use of carbon dioxide as the gas for pneumoperitoneum in 1921, and Case [2] proclaimed pneumoperitoneum as a progressive step in roentgenologic diagnosis. Stewart and Stein,[3] Stein and Arens,[4] Peterson,[5] Lewis,[6] Sante,[7] Faulkner,[8] Martin,[9] and Rubin [10] contributed to improvement of the technique. Most of the credit for emphasizing the diagnostic potentialities of induced pneumoperitoneum

From the Sarah Morris Hospital for Children, the Childrens Endocrine Clinic, and the Department of Obstetrics and Gynecology and the Department of Metabolic and Endocrine Research, Medical Research Institute (supported in part by the Michael Reese Research Foundation), Michael Reese Hospital.

1. Alvarez, W. C.: Use of CO_2 in Pneumoperitoneum, Am. J. Roentgenol. **8**:71 (Feb) 1921.

2. Case, J. T.: Review of 3 Years' Work and Articles on Pneumoperitoneum, Am. J. Roentgenol. **8**:714 (Dec.) 1921.

3. Stewart, W. H., and Stein, A.: Roentgen Ray Study of Abdominal Organs Following Oxygen Inflation of Peritoneal Cavity, Am. J. Roentgenol, **6**:533 (Nov.) 1919.

4. Stein, I. F., and Arens, R. A.: Pneumoperitoneum in Gynecology, Radiology **7**:326 (Oct.) 1926.

5. Peterson, R.: Value of Pneumoperitoneal Roentgenography in Obstetrics and Gynecology, J. A. M. A. **78**:397 (Feb. 11) 1922.

6. Lewis, B. O.: Simplified Apparatus for Induction of Artificial Pneumoperitoneum, Am. J. M. Sc. **211**:84 (Jan.) 1946.

7. Sante, L. R.: Present Status of Pneumoperitoneum as an Aid in Radiological Diagnosis of Abdominal Lesions, Southwestern Med. **11**:529 (Dec.) 1927.

8. Faulkner, W. B., Jr.: Diaphragmatic Hernia and Eventration: Use of Pneumothorax in Differential Diagnosis, Am. J. Roentgenol. **45**:72 (Jan.) 1941.

9. Martin, C. L.: Roentgenologic Studies of Liver and Spleen, Am. J. Roentgenol. **37**:633 (May) 1937.

10. Rubin, I. C.: Subphrenic Pneumoperitoneum, Produced by Intra-Uterine Insufflation of Oxygen as Test of Patency of Fallopian Tubes in Sterility and in Allied Gynecological Conditions, Am. J. Roentgenol. **8**:120 (March) 1921.

and for excellent clinical presentations should be given to Dr. Irving F. Stein [11] and his co-workers. Despite these many contributions, the method has not yet received a wide degree of popularity. Possibly this can be explained by the fact that (1) contraindications and dangers of induced pneumoperitoneum have been overemphasized and (2) that clinicians and radiologists have failed to realize its value.

Recently, Maxfield has emphasized that pneumoperitoneum should be used in conjunction with other clinical and laboratory procedures in those cases in which the diagnosis is obscure. It may confirm clinical impressions when other data are not sufficient for clear-cut diagnosis, or it may completely change the clinical impressions. He states further that pneumoperitoneum is an accurate method of diagnosis enabling the radiologist and/or the clinician to study the outlines of the abdominal and pelvic viscera.[12]

The broad diagnostic value of pneumoperitoneum has been emphasized by Stein recently. He states that "utilizing pneumoperitoneum, we are able to differentiate on the x-ray film between the normal and the abnormal pelvic status. We have been able to distinguish at times the type of pathologic ovarian swelling. . . . Furthermore, absence of the uterus has been shown as well as the presence of uterus, ovaries, and tubes in the absence of the vagina." [11]

In the adult, pelvic examination may reveal significant findings precluding the need for pneumoperitoneum. However, in the child and adolescent, or even the virgin adult, bimanual examination may be physically impossible or impractical. Thus, in these patients, pneumoperitoneum can be of special value in establishing the presence of pelvic anomalies and other pathologic conditions. The procedure is particularly helpful when it appears that a clinical diagnosis cannot be established without laparotomy, and when available laboratory data are inconclusive. It is hoped that the present report dealing with its use in children and adolescents will stimulate new interest and clinical application by others.

MATERIAL AND METHODS

Prior to penumoperitoneum diagnostic studies were performed on all patients according to their individual problems and with the laboratory diagnostic facilities available to us at the time of the study. The various procedures are listed below.

1. History and physical examination
2. Measurements: weight, height, span, symphysis-vertex, symphysis-sole
3. Laboratory: basal metabolic rate, fasting blood sugar; serum cholesterol, cholesterol esters; intravenous insulin tolerance test
4. Hormone excretion: urinary 17-ketosteroids, urinary pregnanediol
5. Vaginal smear for estrogen activity (Schorr stain)
6. X-ray studies: skull (sella turica), bone age, perirenal air insufflation, pneumoperitoneum
7. Endometrial biopsy

11. Stein, I. F.: Gynecopgraphy in the Diagnosis of Ovarian Disorders, in Progress in Clinical Endocrinology, edited by Samuel Soskin, New York, Grune & Stratton, Inc., 1950, p. 374.

12. Maxfield, J. R., Jr., and McIlwain, A. J.: Diagnostic Value of Pneumoperitoneum, Radiology **42**:346 (April) 1944; Pneumoperitoneum in the Study of Pelvic Structures, J. A. M. A. **146**:920 (July 7) 1951.

For a detailed evaluation of laboratory diagnostic methods Wilkins' "The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence" should be consulted.[13]

TECHNIQUE FOR TRANSABDOMINAL PNEUMOPERITONEUM

A urologic radiographic table as described by Dr. Irving F. Stein and Dr. Robert Arens [14] is used, and the following procedures are carried out:

1. High cleansing enema on morning of procedure

2. No breakfast

3. Intramuscular administration of 25 to 100 mg. of meperidine (Demerol) hydrochloride according to weight

4. Bladder catheterization

5. Transabdominal puncture 1 in. (12.5 cm.) below and 1 in. to left of umbilicus using a 20-gauge spinal needle with stylet. The needle is inserted perpendicular to the abdominal wall until the peritoneum is penetrated. A sudden decrease in resistance to the advancing needle signifies penetration. The depth at which this will occur depends on the abdominal wall thickness.

6. Introduction of 300 to 700 cc. (average 500 cc.) of carbon dioxide [15] under 10 to 20 mm. Hg pressure. (Fig. 1*A*)

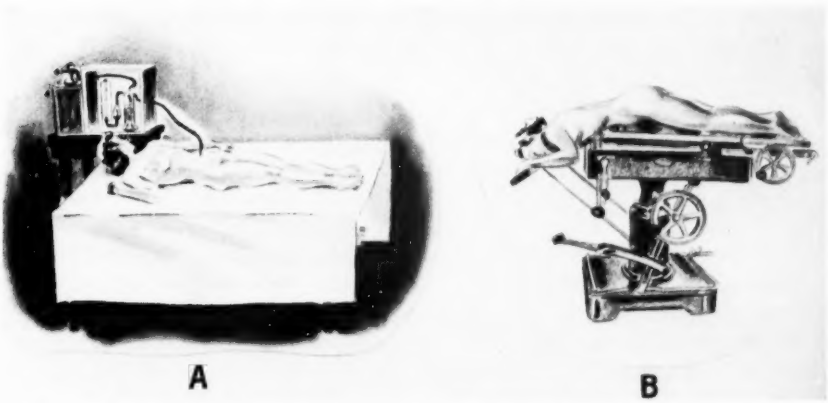

Fig. 1.—Technique of pneumoperitoneum. *A*, introduction of carbon dioxide into peritoneal cavity under 10 to 20 mm. Hg pressure. *B*, patient in modified knee-chest position for radiograph (Stein-Arens Table [14]).

7. Prompt placement of patient in modified knee-chest position as indicated on photograph (Fig. 1*B*)

8. X-ray factors: 65 to 70 kv. 100 ma. 1/10 second.

Thus far, no hazards have been encountered. The procedure is contraindicated (*1*) if the patient has an active intraperitoneal inflammatory process, (*2*) if there

13. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., Charles C Thomas, Publisher, 1950.

14. Stein, I. F., and Arens, R. A.: A Table for Gynecography, Am. J. Obst. & Gynec. **63**:1,169 (May) 1952.

15. Carbon dioxide is absorbed within 12 to 24 hours.

is reason to suspect the presence of bowel adherent to the parietal peritoneum at the site of puncture, (3) if the patient has any cardiac and/or respiratory embarrassment or, (4) if a systemic infection is present.

CLINICAL OBSERVATIONS AND DISCUSSION

Transabdominal pneumoperitoneum was performed in 16 cases[16]; the clinical classification of these is indicated in Table 1. The clinical details are listed in Table 2.

There were eight patients whose principal complaints were failure to grow, failure to menstruate, and absence of secondary sex characteristics (Cases 1 to 8). This triad suggested a differential diagnosis of ovarian agenesis or hypopituitarism. Three cases showed some retardation of osseous development roentgenologically (Cases 4, 5, and 8), and, of these, two showed increased sensitivity to intravenous administration of insulin (Cases 5 and 8). The latter cases fulfilled several of the criteria for the diagnosis of hypopituitarism, namely, delayed growth, absent sec-

TABLE 1.—*Clinical Classification of Cases in Which Transabdominal Pneumoperitoneum was Performed*

	No. Cases
Ovarian agenesis	7
Hypopituitarism, primary	1
Hypo-ovarianism, pituitary	2
Cystic ovary	1
Sexual precocity (constitutional)	2
Pseudohermaphroditism	3
Total	16

ondary sex characteristics, absent menses, delayed osseous development, and increased sensitivity to insulin. In one case (Case 8) small ovaries and an infantile uterus were demonstrated by pneumoperitoneum. This finding, in conjunction with the data mentioned previously, confirmed our earlier impression of hypopituitarism. However, when pneumoperitoneum was employed in Cases 1 to 7, failure to visualize ovaries indicated the diagnosis of ovarian agenesis. Although the estimation of urinary follicle-stimulating hormone would be expected to assist in distinguishing these two types of cases, this hormone assay was not available to us. In order to verify the diagnosis of ovarian agenesis based upon pneumoperitoneum findings, a laparotomy was performed in Case 1. The observations at laparotomy confirmed the roentgen diagnosis. The findings in this case were infantile uterus, no recognizable ovarian tissue on the right, a small area of fibrous tissue in the region of the left ovary, and rudimentary Fallopian tubes. It is apparent from these cases that pneumoperitoneum was a specific measure in the diagnosis of ovarian agenesis.

There were two patients whose chief complaints were lack of development of secondary sex characteristics and failure to menstruate (Cases 9 and 10). Growth and bone age were normal. It was not possible to assay urine for gonadotropins at the time of this study. Pneumoperitoneum in both cases demonstrated ovaries and

16. Some of these patients had a minimal amount of discomfort consisting of shoulder pain of several hours' duration.

uteri which were smaller than normal. On the basis of these findings, hypo-ovarianism due to lack of pituitary gonadotrophic stimulation appeared to be the most likely diagnosis.

One of our patients, E. J. (Case 11), age 13 years, complained of excessive vaginal bleeding for three weeks followed by failure to menstruate for two months. Her physical development was normal. The symptoms were suggestive of cystic ovary, bilateral polycystic ovaries (Stein-Levanthal syndrome),[17] or ovarian dysfunction without gross anatomic change. Laboratory findings were normal except for a persistently high estrogen activity in the vaginal smears. Pneumoperitoneum revealed an enlarged ovarian mass, which we interpreted as a cystic right ovary. This finding, in conjunction with the vaginal smears, led us to believe that the menstrual disturbance was a result of an estrogen-producing cyst. The patient received no hormonal therapy, and after 18 months of amenorrhea, rhythmic menses were reestablished. Thus, it is evident from this case that pneumoperitoneum can be used to reveal ovarian enlargements.

Two patients, H. K., age 10 years (Case 12), and M. F., age 7 years 9 months (Case 13), presented evidence of sexual precocity. H. K. complained of vaginal bleeding for six weeks. On physical examination the secondary sex characteristics were noticeably advanced beyond that expected for her chronological age. Her bone age was 15 to 17 years. Findings on an x-ray of the skull were normal. Vaginal smears indicated high estrogen activity. Vaginoscopic examination showed no local pathology to account for the bleeding. Biopsy revealed a proliferative endometrium. The pneumoperitoneum demonstrated a normal-appearing adolescent uterus and ovaries. M. F. was studied because of breast development and growth of pubic hair beginning before the seventh year (Fig. 2). Her bone age was 12 to 14 years. X-ray of the skull was normal. High estrogen activity was shown by the vaginal smears. Pneumoperitoneum revealed a normal-appearing adolescent uterus and ovaries (Fig. 2*A*). In both of these cases the differential diagnosis initially rested between sexual precocity due to a functioning ovarian tumor and ovarian dysfunction of a constitutional nature.[18] Pneumoperitoneum in both instances indicated normal-appearing uteri and ovaries. Thus, pneumoperitoneum proved of value in excluding ovarian tumor in both cases and led us to conclude that the sexual precocity was in all probability due to a constitutional disturbance.

The final group consisted of three patients with abnormalities of the external genitalia. G. G. (Case 14), a 21-month-old infant, had been observed from birth. The significant findings were average height and weight for age, hypospadias or a hypertrophied clitoris adherent posteriorly, a dimple 1 cm. below the urethral orifice, bifid empty scrotum, a pea-sized mass in the right inguinal region, and an empty left inguinal canal. Pneumoperitoneum revealed that the pelvis contained no genital structures. These findings suggested that the child was a male pseudo-hermaphrodite. However, a definitive diagnosis awaits exploration of the right inguinal mass, which will be carried out at a later date.

17. Stein, I. F., and Leventhal, M. L.: Amenorrhea Associated with Bilateral Polycystic Ovaries, Am. J. Obst. & Gynec. **29**:181 (Feb.) 1935.

18. Novak, E.: The Constitutional Type of Female Precocious Puberty with a Report of 9 Cases, Am. J. Obst. & Gynec. **47**:20 (Jan.) 1944.

TABLE 2.—*Summary of Clinical Data*

Case	Patient	Age, Yr.	Sex	Principal Complaints	Physical Findings	Pertinent Laboratory Data	Pneumoperitoneum	Final Diagnosis
1	P. L.	14	F	Failure to grow; failure of breast development	Ht. 53 in. (134.6 cm.), wt. 77 lb. (30.4 kg.); fine pubic hair; no axillary hair; absent breast development; infantile vulva and vagina	Normal bone age	Absent ovaries and minute uterus	Ovarian agenesis
2	C. P.	14	F	Failure to grow; failure to menstruate	Ht. 48 in. (121.9 cm.), wt. 60 lb. (27.2 kg.); high palate; absent breast development; absent axillary hair, scant pubic hair; infantile external genitalia	Normal bone age	Absent ovaries and minute uterus	Ovarian agenesis
3	M. W.	18	F	Failure to menstruate; overweight	Ht. 57½ in. (146.0 cm.), wt. 150 lb. (68.0 kg.); sole-symph. 30½ in. (77.5 cm.), symph.-crown 27 in. (68.6 cm.), span 61½ in. (156.2 cm.); general obesity; minimal secondary sex characteristics (previous estrogen treatment); infantile external genitalia	Normal bone age; vaginal smear, absence of estrogen activity; 17-ketosteroids, 3.1 mg./24 hr.	Absent ovaries and minute uterus	Ovarian agenesis (confirmed by laparotomy)
4	F. B.	19	F	Failure to grow; failure to menstruate; no breasts	Ht. 53 in., wt. 86 lb. (39.0 kg.); webb neck; infantile breasts; slight development of external genitalia; sparse sexual hair; vaginoscopic exam., infantile vagina	Bone age, slight retardation; vaginal smear, absence of estrogen activity; pregnanediol, 0.13 mg./24 hr.; prolan, 25 RU/24 hr.; 17-ketosteroids, 2.8 mg./24 hr.	Absent ovaries and minute uterus	Ovarian agenesis
5	E. C.	23	F	Failure to grow; failure to menstruate; no breast development	Ht. 53 in., wt. 80 lb. (36.3 kg.); no breast development; no axillary hair, normal pubic hair; infantile external genitalia	Bone age, 16 to 17 yr.; vaginal smear, absence of estrogen activity; fasting blood sugar, 42 mg./100 cc.; increased sensitivity to insulin (0.05 U./kg. I. V.)	Absent ovaries and minute uterus	Ovarian agenesis
6	M. B.	12	F	Failure to grow	Ht. 48 in., wt. 53 lb. (24.0 kg.); undeveloped breasts; no sexual hair; high palate; increased carrying angle; keratitis	Bone age normal; Kahn ++++ in spinal fluid; vaginal smear, absence of estrogen activity	Absent ovaries and minute uterus	Ovarian agenesis; congenital syphilis
7	M. R.	18	F	Failure to grow; failure to menstruate	Ht. 55 in. (139.7 cm.), wt. 109 lb. (49.4 kg.); increased carrying angle; scant sexual hair; infantile breasts; obesity	Bone age, normal; vaginal smear, absence of estrogen activity	Absent ovaries and minute uterus	Ovarian agenesis
8	E. Z.	19	F	Failure to menstruate; failure to grow	Ht. 52 in. (132.1 cm.), wt. 85 lb. (38.6 kg.); juvenile appearance; normal body proportions; sparse pubic and axillary hair; juvenile genitalia; obesity; hypoplastic breasts	Bone age, some retardation; fasting blood sugar, 96 mg./100 cc.; insulin tolerance (0.05 U./kg. I. V.); blood sugar 0 in 40 min.; cholesterol, 156; esters, 63%; BMR, −8.5%; PBI, 5.5 g; vaginal smear, no estrogen activity; pregnanediol 0.05 mg./24 hr.	Small ovaries and infantile uterus	Primary hypopituitarism
9	D. L.	17	F	Failure to menstruate; absent secondary sex characteristics	Normal height and weight; congenital deformity of the face; no breast development; no sexual hair; juvenile vagina	Bone age, normal; vaginal smear, no estrogen activity	Small uterus and ovaries	Hypo-ovarianism, pituitary

TABLE 2.—*Summary of Clinical Data—Continued*

10	N. T.	17	F	Failure to menstruate; not developing sexually	Normal stature; juvenile appearance; infantile breasts; scant axillary hair; hypoplastic external genitalia; smooth hyperemic vagina	Bone age, normal; BMR, + 12%; endometrial biopsy, proliferative endometrium; vaginal smear, no estrogen activity	Small uterus and ovaries	Hypo-ovarianism, pituitary
11	E. J.	13	F	Excessive vaginal bleeding for 3 wk. followed by failure to menstruate for 2 mo.	Ht. 62 in. (157.5 cm.), wt. 116 lb. (52.6 kg.); normal female development	BMR, + 3%; cholesterol, 149; esters, 73%; vaginal smears, peristent high estrogen activity	Enlarged right ovary	Cystic right ovary
12	H. K.	10	F	Vaginal bleeding 6 wk.	Short stature 53½ in. (135.9 cm.), 85 lb.; crown-pubis 30 in. (76.2 cm.); sole-pubis 23½ in. (59.7 cm.); mature appearance; well-developed breasts; steatopygy; permanent teeth erupted	Bone age, 15-17 yr.; BMR, + 19.2%; vaginal smear, high estrogen activity; endometrial biopsy, proliferative endometrium	Normal adult uterus and ovaries	Constitutional sexual precocity
13	M. F.	7 9/12	F	Breast development and pubic hair for 9 mo.	Mature appearance; adolescent breasts with areola pigmented; abundant pubic hair; pigmented vulva, normal fat pads; well-developed fossa navicularis and rugation of vagina	Bone age, 12-14 yr.; vaginal smear, high estrogen activity	Adolescent uterus and ovaries	Constitutional sexual precocity
14	G. G.	1 9/12	M	Abnormal external genitalia	Average height and weight for age; hypospadias or hypertrophied clitoris; phallus adherent posteriorly; dimple 1 cm. below urethral orifice; vaginal meatus (?); bifid empty scrotum; pea-sized mass in right inguinal region; left inguinal canal empty; no sexual hair; no urogenital sinus	Normal bone age	Absence of female pelvic structures	Probable male pseudohermaphrodite
15	S. S.	5	♀	Hair growth near penis; abnormality of genitalia and undescended testes	Taller than normal for age; coarse abundant pubic hair; few axillary and chest hairs; penis-like structure with urethral opening at base of shaft; bifid scrotum-like structure; rugated scrotal folds	Bone age, 14 yr.; pregnanediol, 99 mg./24 hr.; perirenal air insufflation, normal-appearing adrenals	Uterus and ovaries visualized	Female pseudohermaphrodite; adrenogenital syndrome
16	W. K.	23	M	Gastrointestinal complaints	Ht. 62 in., span 66 in. (167.6 cm.); sparse beard; gynecomastia; sparse axillary hair; female distribution of pubic hair; hypospadias; cleft scrotum; right gonad small and sensitive; 3 masses palpable in left inguen; left scrotal hernia; perineal dimple 5 mm. deep; small prostate	Bone age, normal; 17-ketosteroids, 5-6 mg./24 hr.; perirenal air insufflation; normal adrenals	No female pelvic structures visualized	Probable male pseudohermaphrodite (exploration left inguen contents — Fallopian tube, testis, epididymis; right inguen not explored)

S. S. (Case 15), a 5-year-old child, was observed at birth to have an abnormality of the genitalia and absent testes. Pubic hair began to grow at the age of 3 years. At 5 years the pertinent physical findings were a child taller than normal for the chronological age, few axillary and chest hairs, coarse abundant pubic hair, a penis-like structure with a urethral meatus at its base, and a bifid rugated empty scrotum. The significant laboratory data were a bone age of 14 years, a urinary excretion level of pregnanediol, of 99 mg. per 24 hours, (normal less than 1 mg. per 24 hours). The adrenals appeared normal by perirenal air insufflation. Pneumoperitoneum demon-

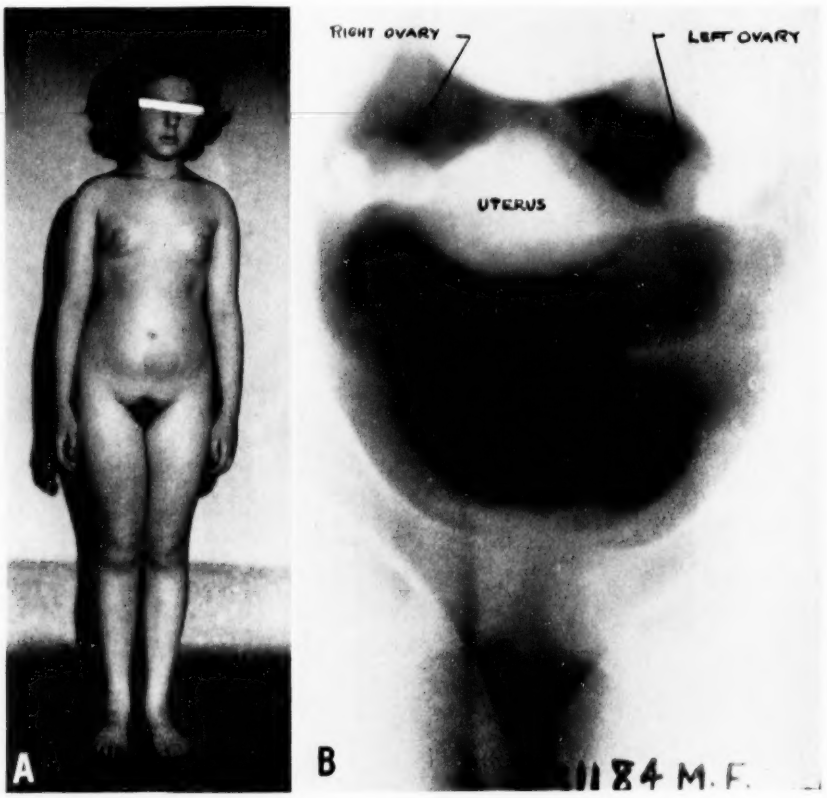

Fig. 2.—M. F. (Case 12), age 7 years, 9 months. Constitutional sexual precocity. *A*, photograph of patient, showing adolescent breasts, abundant pubic hair. *B*, pneumoperitoneum showing normal adolescent ovaries and uterus.

strated normal-appearing juvenile uterus, tubes, and ovaries. Exploration of the left adrenal revealed a large gland. Biopsy showed hyperplasia of the cortex. Thus, the pneumoperitoneum in this case indicated that we were dealing with a female pseudohermaphrodite. Furthermore, the clinical and laboratory findings were characteristic of adrenal cortical hyperplasia.

W. K. (Case 16), a 23-year-old person, was referred to us for evaluation of anomalies of the external genitalia. The body proportions were eunuchoid. On

physical examination the following findings were noted: sparse beard, gynecomastia, sparse axillary hair, feminine distribution of pubic hair, hypospadias, cleft scrotum with an indirect inguinal hernia on the left, a perineal dimple 5 mm. deep, and a right inguinal mass, small and sensitive to the touch. In the left inguinal region, three discrete small masses were palpated. The prostate was small. Pertinent laboratory data were 17-ketosteroid urinary excretion 5 to 6 mg. per 24 hours (normal 10 to 20 mg. per 24 hours), bone age normal. Perirenal air insufflation demonstrated normal-appearing adrenals. Pneumoperitoneum revealed no female pelvic structures. The surgeon who did an exploratory operation at another hospital reported the presence of a Fallopian tube, testis, and an epididymis in the left inguinal region. The right inguinal region was not explored. Although the nature of the right inguinal mass was not determined, the presence of a testis on the left and the failure to visualize female genital structures by pneumoperitoneum led us to conclude that this patient was probably a male pseudohermaphrodite.

Although pneumoperitoneum was of definite value in establishing a diagnosis in the case of the female pseudohermaphrodite, this procedure provided presumptive evidence in the case of the two suspect male pseudohermaphrodites. In the latter cases surgical exploration and histologic study of the inguinal masses are necessary to confirm the impressions gained by pneumoperitoneum.

SUMMARY AND CONCLUSIONS

In some sex-endocrine disturbances, detailed physical examination as well as available laboratory studies may be diagnostically inconclusive. In such cases transabdominal pneumoperitoneum may aid in establishing the clinical diagnosis and thus avoid laparotomy. The method is of special value in the study of children with such disturbances because of the difficulty of adequate pelvic examination. Furthermore, early diagnosis is desirable in order to plan future medical and/or surgical management.

The technique consists of introducing a measured amount of CO_2 into the peritoneal cavity and then visualizing roentgenographically the outlines of the pelvic viscera.

The patients in 16 cases, which include ovarian agenesis, precocious puberty, hypopituitarism, hypo-ovarianism, cystic ovary, and intersexuality, have been studied by this technique.

ADDENDUM

Recently we successfully performed pneumoperitoneum on an 11 week old infant with pseudohermaphroditism. Female pelvic structures were clearly demonstrated. No untoward symptoms resulted from the procedure.

Dr. Morton Andelman gave permission for Case 12 to be reported and Dr. Alvin C. Rambar for Case 15. This case is to be published in detail by Dr. Rambar.

QUANTITATIVE VARIATIONS IN THE RESPIRATION OF THE NEWBORN INFANT

PHILIP J. HOWARD, M.D.
AND
A. ROBERT BAUER, M.D.
DETROIT

ADDITIONAL observations have been made on the respiration of 14 sleeping newborn infants ranging in age from 8 days to 46 days, in an effort to reexamine the trend and range of normal with reference to minute volume, tidal air, rate, and pattern. The observations have been related to the weight of the infant, and in some instances to the body surface. It is hoped that a contribution toward a better understanding of the normal trend and range of the respiration of the newborn infant during sleep will be obtained from this material so that a proper interpretation may be made when a stimulating gas is administered. Certain records have been analyzed by 10-second periods within the total minute to show that the volume of air breathed is at all times an astatic or changing quantity. Although we confirmed the statement of Cross [1] and Boutourline-Young [2] that the average infant required approximately 20 minutes to reach a baseline, we were impressed with the individual variation and even had some examples of infants who while sleeping simply increased in minute volume exchange during the entire observation.

Since the publication of our last article in 1949,[3] articles have appeared on this subject describing newer techniques and some improvements in the apparatus (plethysmograph). These newer techniques, together with statistical analysis of the results seen, were felt to offer more accurate information regarding the physiology of respiration in these young subjects. We too have made some changes in our apparatus. Like the other investigators in this field, we were not satisfied with the efficiency of the sponge rubber collar seal around the baby's neck. Cross [4] allowed the infant's face to protrude through an opening in the plethysmograph using an inflatable rubber seal between the infant's face and the edge of the opening. Boutourline-Young and Smith [2] employed an inflatable collar around the infant's neck and a soft rubber sleeve to prevent leaks. In the present study, we used a com-

From the Department of Pediatrics, the Henry Ford Hospital.

1. Cross, K. W., and Warner, P.: The Effect of Inhalation of High and Low Oxygen Concentrations on the Respiration of the Newborn Infant, J. Physiol. **114**:283 (July) 1951.

2. Boutourline-Young, H. J., and Smith, C. A.: Respiration of Full Term and Premature Infants, Am. J. Dis. Child. **80**:753 (Nov.) 1950.

3. Howard, P. J., and Bauer, A. R.: Irregularities of Breathing in the Newborn Period, Am. J. Dis. Child. **77**:592 (May) 1949.

4. Cross, K. W.: Plethysmograph for Studying Respiration in the Newborn Infant, J. Physiol. **108**:37 (May) 1949.

TABLE 1.—*Data on Fourteen Infants Studied During Sleep**

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17†	18‡
		Birth		Day of Observation				Blood Examination§			Observations During 20th-30th Min. of Sleep						
											Minute Volume, Cc.					Min. Vol., Cc./Kg. Body Weight	Min. Vol., Cc./Sq. M. Body Surface
Case	Patient	Date	Weight, Kg.	Age, Days	Height, Cm.	Weight, Kg.	Body Surface Sq. M.	HBG, Gm./100 Cc.	RBC, Million	W. B. C.	Average	High	Low	Resp. Rate, Average	Tidal Air, Average in Cc.		
1	R. B.	10/ 4/51	2.779	40	51	3.404	0.210	13.1	3.8	13,700	690.0	825.4	626.6	56.5	12.2	202.7	3,285.7
2	B. B.	9/20/51	3.544	12	51	3.686	0.220	17	4.4	10,650	760.6	.....	.....	58	13.1	214.6	3,457.2
3	P. C.	9/ 7/51	3.544	17	51	3.658	0.219	10.2	3.3	11,350	897.8	1,053.5	810.2	39.4	23.4	245.4	4,099.5
4	M. C.	9/27/51	2.807	12	50	3.233	0.201	18.7	5.2	10,200	686.3	769	641	38.5	18.1	212.1	3,414.1
5	T. E.	8/ 3/51	3.205	15	53	3.489	0.219	14.6	4.8	8,200	1,148.3	1,736.6	965.9	43.6	26.2	327.3	5,020.5
6	L. G.	6/17/51	3.233	13	51	3.290	0.209	11.3	3.7	7,800	559.6	.....	.....	26	21.5	170.0	2,677.5
7	F. G.	8/28/51	3.262	14	53	3.489	0.219	15.5	4.9	14,250	796.0	.....	.....	26	30.6	228.1	3,132.3
8	D. H.	8/ 2/51	3.006	12	49	3.120	0.194	12.1	3.8	8,000	825.2	952.4	693.8	42.9	19.3	264.4	4,253.6
9	P. M.	11/26/51	2.665	17	51	2.665	0.188	13.0	3.8	9,700	545.7	583.7	481.0	44.7	12.2	204.7	2,902.6
10	J. M.	8/ 9/51	2.722	40	47	2.864	0.182	10.4	3.1	10,100	862.2	960.7	814.4	56.4	15.2	301.0	4,748.6
11‖	S. P.	6/22/51	1.648	46	47	2.921	0.183	12	3.0	8,400	822.3	863.3	814.0	51.5	16.1	281.4	4,469.0
12	R. S.	11/ 2/51	2.665	33	48	3.290	0.198	15	4.7	7,850	729.0	904.8	590.5	60.1	11.9	221.5	3,681.8
13	D. S.	11/ 2/51	2.637	19	50	2.779	0.189	12.5	4.3	10,150	454.8	487.5	381.2	50.1	8.9	163.6	2,405.3
14	R. W.	6/10/51	2.779	8	47	2.779	0.180	12.5	4.1	10,800	953.9	.....	.....	54	17.6	343.2	5,299.4
Average		.....	.....	..	50.9	3.190	0.201	...	...	.....	766.1	913.6	681.8	46.3	16.9	241.4	3,774.0

* Minute volumes given are averages observed during 20th to 30th minutes of sleep, inclusive.
† Figures obtained by dividing figures in Column 12 by those in Column 7.
‡ Figures obtained by dividing figures in Column 12 by those in Column 8.
§ Blood values show the infants to be normal in this respect.
‖ Included because the infant, although premature, was 46 days old and the size of the others in the group.

mercially produced plastic collar currently supplied with one of the Drinker respirators. It is a large tube of plastic material supported on two metal rings, one at either end. As one end is held stationary and the other end rotated, the diameter of the opening closes down in the same manner as the diaphragm of a microscope condenser. The edge of the opening was a little too rigid and sharp for the baby's neck, and so we interposed an inflatable rubber collar between it and the neck. This reduced the tendency to leakage and caused no discomfort to the infant. We made no change in the recording system. Also, there was no change in our technique of obtaining the record. The infant was placed in the plethysmograph, and as soon as he was sleeping soundly and quietly, the recording system was started and was continued without interruption until the test was terminated. This procedure gave us satisfactory tracings which varied in length of time from 20 to 60 minutes. Each calculation of minute volume was done on a full minute of record. Where possible, we calculated the 1st, 5th, 10th, and 15th minute in the first 20-minute period of sleep in the plethysmograph, which has been designated as the

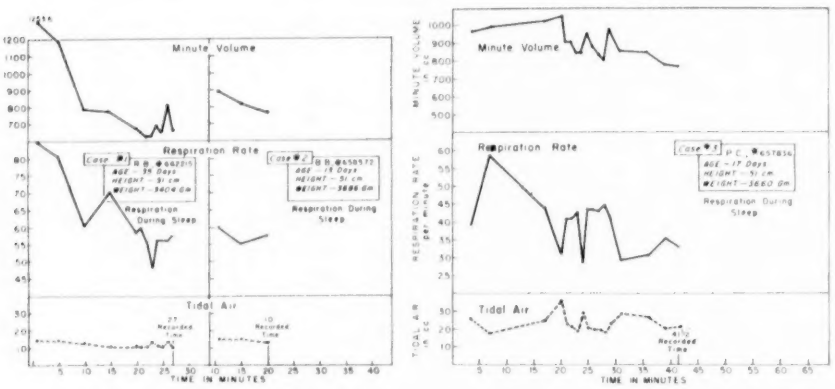

Chart 1.—Values for minute volume, rate, and tidal air in Cases 1, 2, and 3.

acclimation period. We then calculated each available minute from the 20th to the 30th minutes, this period being considered one in which the infant was in a basal state. From that point to the end of the experiment we attempted to calculate each fifth minute.

The observation results are shown in Table 1, which includes weight, height, and body surface. The normalcy of the infants is indicated by blood reports, to supplement careful physical examinations. The respiratory minute volume is indicated as well as the highest and lowest variation for each infant. The rate and tidal air are included and finally the minute volume per unit of weight and body surface. Individual graphs were made for each infant, showing the time in minutes on the abscissae and the values for minute volume, rate, and tidal air on the ordinates. These are reproduced in Charts 1 to 5. Examination of the graphs gives a clear picture of the variations which occur from minute to minute, but it does not show that which takes place within the minute itself.

Since irregularity is such a constant feature of respiration in the newborn infant, we attempted to get more critical data on this aspect of the study, especially as it

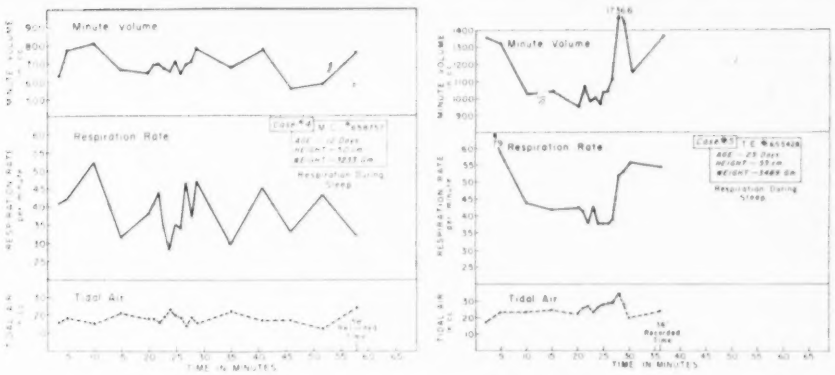

Chart 2.—Values for minute volume, rate, and tidal air in Cases 4 and 5.

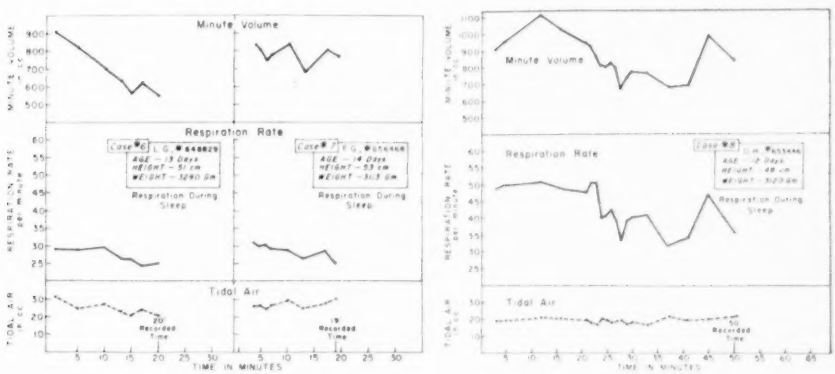

Chart 3.—Values for minute volume, rate, and tidal air in Cases 6, 7, and 8.

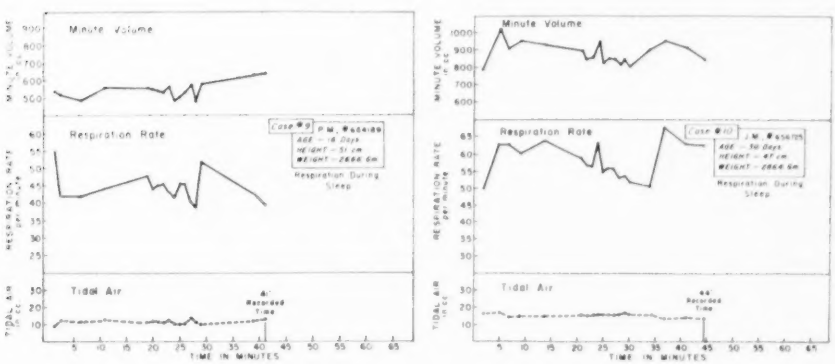

Chart 4.—Values for minute volume, rate, and tidal air in Cases 9 and 10.

might influence those figures which have already been established as basic measurements in this field. Respiratory rate and tidal air have received much attention, but most of the recent work has been done on measurements of minute volume which

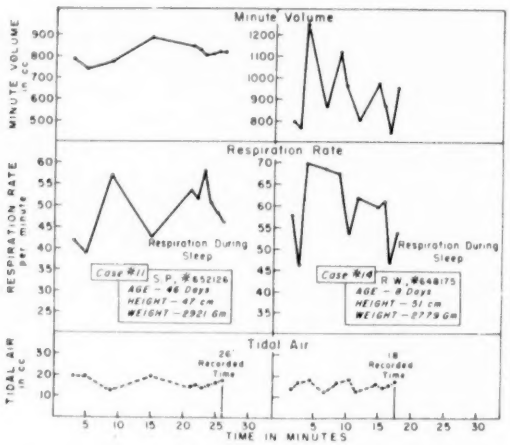

Chart 5.—Values for minute volume, rate, and tidal air in Cases 11 and 14.

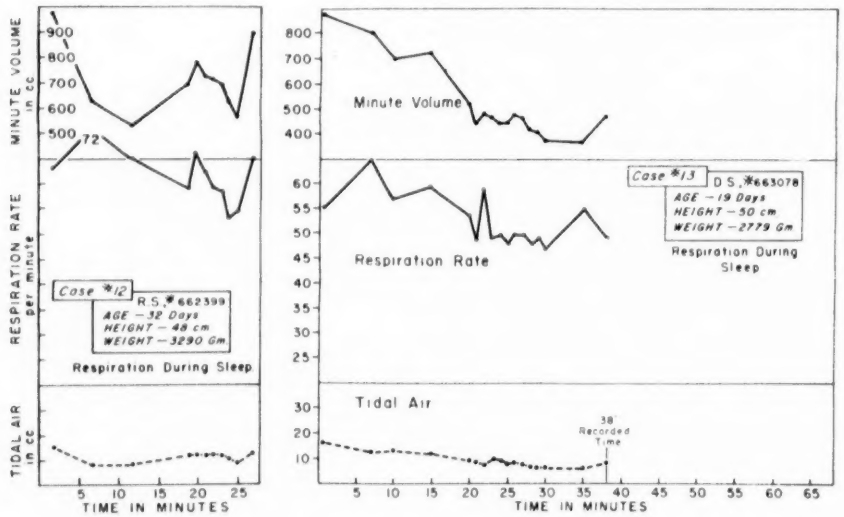

Chart 6.—Values for minute volume, rate, and tidal air in Cases 12 and 13.

is the sum of tidal inspiration in a given minute. This measurement seems to have been accepted by common consent as a good unit for purposes of investigation. We were interested in finding out whether it was the best unit for newborn infants, rather than some other unit of time such as 10 seconds, 30 seconds, or a much longer time like six or eight minutes. It is obvious that the greatest variation will occur

when individual respirations are compared with each other, ranging all the way from the zero of apnea up to the 40 cc. of a sigh, but when groups of respirations are compared with other groups, the variation will be less. In the case of minute volume, the group of respirations is that number which occurs in a minute (about 40).

To test the soundness of this reasoning, we picked four of our most satisfactory tracings and used only that portion of them between the 20th and 30th minutes as representing a basal state. In all, there were 38 minutes of actual tracing, 8 from Case 1, 9 from Case 5, 10 from Case 8, and 11 from Case 13. Each of the 38 minutes was treated as follows: We calculated the amount of air breathed in a 10-second period and multiplied it by six, which gave us a "minute volume" during that 10-second period. The other 10-second periods in that minute were calculated in the same way. Then taking the observed minute volume for the entire minute

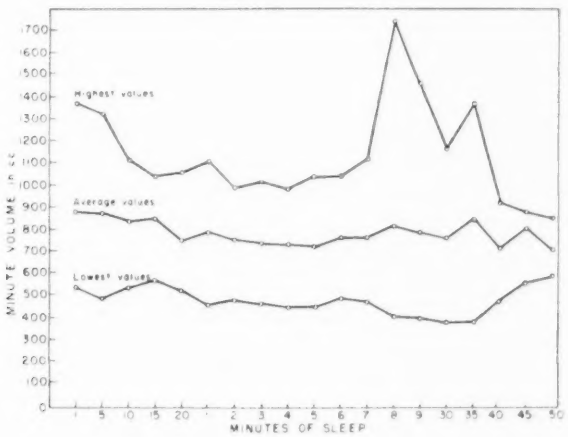

Chart 7.—Average respiratory minute volume of 14 infants during sleep and the minute of sleep observed. The 20th to 30th minutes are relatively basal. Range is also shown. Note the disproportionate elevation of the highest value in Minute 28 was due to Case 5, as shown in Table 2.

as a standard, and comparing the "minute volumes" from each 10-second period in that minute with it, we showed variations which averaged 34.5%. Calculating in the same way using 30-second periods, the variation averaged 19.9%. Using 60-second periods for these four selected cases, the variation was 38%. Using the entire series from Table 1, the variation was 30%.

These results would seem to confirm the frequently repeated statement that a certain amount of irregularity is inherent in the respiratory pattern of the newborn infant. Also, it appears that the 20-minute acclimation period in the plethysmograph will not eliminate or materially reduce it. The fact that there was less variation when the minute volume was calculated on a 30-second period basis than when 10 seconds were used suggests that not less than 30 seconds of a tracing should be used for this purpose. By this same token, nothing would be gained by using more than one minute of a tracing for the calculation, since there was no further reduction in the amount of variation when the comparisons were made between the one-minute periods occurring in a 10-minute segment.

TABLE 2.—*The Minute Volume During Sleep of Fourteen Infants, Showing the Minutes of Sleep*

Case No.	Patient	Minutes of Sleep																	
		Minute Volume																	
		1-4	5	10	15	20	21	22	23	24	25	26	27	28	29	30	35	40	45
1	R. B.	1,253.6	1,194.3	792.4	785.8	685.5	676.2	639.6	640.5	700.9	680.1	825.4	675.5	.....	.....	.....	.....	.....	.....
2	B. B.	.....	.....	892.2	818.3	760.6	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
3	P. C.	.....	966.2	989.5	1,033.4	1,053.5	907.5	908.2	842.9	842.7	955.5	844.1	842.4	810.2	976.9	852.7	849.3	783.3	.....
4	M. C.	625	779.0	806.0	671.0	644.0	692.0	695.0	674.0	654.0	701.0	641.0	689.0	704.0	769.0	.....	674.0	768.0	560.0
5	T. E.	1,366	1,323.3	1,087.4	1,046.3	965.9	1,083.6	991.8	1,010.0	981.3	1,040.3	1,044.4	1,112.1	1,736.6	1,453.8	1,156.9	1,369.9	.....	.....
6	L. G.	909.1	825.1	717.4	568.0	559.6	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
7	F. G.	829.5	809.7	837.8	696.7	796.0	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
8	O. H.	907.9	967.8	1,105.1	1,029.3	.....	952.4	932.7	877.1	820.2	814.7	830.8	800.8	693.8	741.9	788.4	777.8	704.6	988.4
9	P. M.	544.5	493.2	561.0	.....	569.8	566.2	554.9	543.4	572.5	481.0	507.5	549.7	579.0	495.6	583.7	.....	628.8	.....
10	J. M.	778	1,017.8	939.6	931.5	.....	866.5	859.4	869.1	960.7	835.8	856.0	847.8	825.0	847.8	814.4	902.9	922.0	879.7
11	S. P.	795.2	743.3	778.5	880.6	.....	863.3	844	814	816.5	820.6	820.4	.....	.....	.....	.....	.....	.....	.....
12	R. S.	982.0	633.2	535.6	.....	792.6	747.6	731.4	706.2	630.1	590.5	.....	904.8	.....	.....	.....	.....	.....	.....
13	D. S.	869.8	803.1	706.4	723.8	527.5	457.5	486.1	470.0	453.1	455.0	487.5	472.5	410	402.5	381.2	382.5	475.0	.....
14	R. W.	709.8	868.9	961.8	972.1	953.9	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
	Average	888.3	878.0	832.9	846.4	755.3	784.2	764.0	744.7	743.2	737.4	766.3	766.0	822.6	812.5	762.8	826.0	713.6	809.3
	Low	544.5	493.2	535.6	568	527.5	457.5	486.1	470.0	453.1	455	487.5	472.5	410.0	402.0	381.2	382.5	475.0	560.0
	High	1,366	1,323.3	1,105.1	1,046.3	1,053.5	1,083.6	991.8	1,010.0	981.3	1,040.3	1,044.4	1,112.1	1,736.6	1,453.8	1,156.9	1,369.9	922.0	879.7

Table 2 lists all of the calculated minute volumes placed in columns corresponding to the time during the test when they occurred, the time being measured in minutes and the start of the recording being zero minutes. Averages for each time interval appear at the bottom of the columns. Chart 7 presents this material in graphic form, the middle line representing the averages, the upper, the highest figure for that minute, and the bottom line, the lowest. This chart confirms the impression that on the average respiration minute volume falls in 20 minutes to a comparative basal level.

Table 3 lists the lowest minute volume from each infant together with the time (number of minutes asleep in the apparatus) when it was obtained. It will be noted that not all of them occurred during the 20th- to 30th-minute "basal state." Actually, seven occurred during this time, five before, and two after. An average

TABLE 3.—*Lowest Minute Volume Recorded in Each Infant's Record and Particular Minute Observed of Sleep in Which it Occurred**

Case No.	Lowest Minute Volume, Cc.	Minute of Sleep of This Observation
1	636.6	22
2	760.6	20
3	783.3	40
4	560.0	45
5	965.9	20
6	559.6	20
7	696.7	15
8	693.8	28
9	481.0	25
10	778.0	1
11	743.3	5
12	535.6	10
13	581.2	30
14	790.8	1
Average	669.6	
Average body weight	3.190 kg.	
Average body surface	.201 sq. m.	
Average min. vol. kg	2,001 cc.	
Average min. vol. sq. m.	3,331.3 cc.	

* Six of the values were outside of the period of the 20th to 30th minute.

of all of these lowest figures was included in Table 4 for comparison with the published averages as well as our own averages for this series. We wonder if the lowest figure for each infant does not represent a truer basal state than any average of figures taken from an arbitrarily chosen period of sleep during which the baby may be disturbed by any one of a number of stimuli such as noise, gas pains, voiding, passing a stool, changing position, and many others sufficient to alter the respiratory pattern without waking the baby or even giving evidence to the observer that anything was amiss.

The basic data on minute volume seem quite variable when consideration is given to every analyzable record on infants who are asleep. To obtain a series of records all of which show a decline to a basic state in 20 minutes requires the refusal of a great number. In this short series there are five which did not follow the pattern of coming to a basal resting state in 20 minutes. As this is a difficult measurement to make, the observer may unconsciously select the quietest infant in the nursery, but whether because the quietest and most easy to handle it is the most

normal infant is questionable or uncertain. The results of our observations, if they can be for the moment expressed with a few words, are the conclusions that respiration is of multiple patterns, that its component parts, rate, and tidal air have a wide range, and that volume per 10-second period, per 30-second period, and per minute is variable, even within the limits of sleep.

The chief purpose of this work was to further establish criteria of normalcy in the respiratory variations so that one might more properly evaluate the data obtained from experiments in which these variations are influenced by the administration of different mixtures of oxygen or other gases. It is our opinion that until we are able to understand the irregularities which occur normally in newborn infants, we shall not be in a position to devise intelligently any form of treatment for those pathological conditions with which respiratory irregularity is often associated. To state it another way, we feel that the irregularities which occur normally are physiological variations which are purposeful, and that their association with pathological conditions is a simple extension of that physiologically useful mechanism attempting to readjust an altered blood chemistry towards normal by quantitating

TABLE 4.—*Published Data on Comparative Minute Volume Averages*

	Average Minute Volume, Cc.	Minute Volume, Cc./Kg.	Minute Volume, Cc./Sq. M.
Cross [1]	589*	170*	.....
Howard and Bauer [3]	731	250	.....
Boutourline-Young and Smith [2]	642	182	2,819
Howard and Bauer	766.1	241	3,774
	669.6†	209	3,331

* Figures taken from Boutourline-Young and Smith.[2]

† Average of the lowest minute volume obtained from each of the 14 infants, irrespective of the minute this value occurred, whereas the figure 766.1 cc. was an average of all minute volumes during the 20th to 30th minutes from all 14 infants.

the output of CO_2 against that other important function of respiration, the uptake of O_2. It is inconceivable to us that the amount of O_2 required by the body will always bear a constant relationship to the amount of CO_2 which must be given off. In a previous communication we described the manner in which we thought this quantitation was achieved by the different respiratory patterns, and we believe that the matter is sufficiently important to justify referring to it again.

The matter of using the lowest minute volume as representing a basal figure rather than an average would seem to merit some thought. The greatest advantage would be that, being lowest, it is basal by definition. Another is that being a very short period of time, one minute, it is likely that it was obtained at a time when the infant was not being stimulated in any way. The obvious disadvantage of using such a single figure as a basis of estimating the effect of an administered gas is the time element. To assess the effect of administered gas, the preceding minutes must be used, whether they were in fact basal or not. The use of averages of the preceding minutes would tend to equalize the extremes which might occur from extraneous stimulation and would therefore appear to be the preferable method, provided the worker made due allowance for the error involved in his final interpretation of the results.[5]

5. Howard, P. J., and Bauer, A. R.: Respiration of the Newborn Infant: Variation in Respiratory Minute Volume with Change in Per Cent of Oxygen in Respired Mixture, Am. J. Dis. Child. **79**:611 (April) 1950.

TUBERCULOUS PERICARDITIS IN CHILDREN

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TWO FACTS have stimulated our interest in tuberculous pericarditis. First, and most important, there are indications that this disease is becoming amenable to treatment and may also be seen in early stages more often because of therapy of tuberculosis elsewhere. Second, the literature ascribes to acid-fast bacilli the major role in the production of adhesive pericarditis. This has appeared unlikely to us in the past, as it has occurred so rarely in tuberculous children seen at this hospital. It is true that in one of our cases the diagnosis was missed clinically, but in a survey of cases with autopsy in the past 30 years, this was the only one in which the diagnosis was not made ante mortem.

There have been 136 autopsies done on tuberculous children in the past 30 years. Six instances of tuberculous pericarditis were found. In five others a pathological diagnosis of the disease was recorded, but the evidence to confirm this diagnosis was slight. The pericardial involvement found consisted in the presence of a few epicardial miliary tubercles. It is of interest to note here that in one of these clinical cases (Case 5) the patient was known to have small epicardial tubercles two months before death, when cardiac arrest needing thoracotomy allowed palpation and visualization of their presence. When death occurred two months later, after treatment with streptomycin and *p*-aminosalicylic acid, no tubercles were found. Pericardial tubercles are found much less frequently than are those of other serous surfaces in patients dying of miliary tuberculosis. When they are seen, similar lesions are usually found in the chordae tendineae.

The myocardial involvement found in these cases at autopsy might be mentioned here. It has been noticed by many observers to be conspicuous by its absence. With one exception (Case 4), changes other than slight hypertrophy of the muscles were not seen in any of this series of cases of adhesive pericarditis. Pallor and firmness of the heart muscle was noted twice in cases of pulmonary tuberculosis. In two miliary cases with involvement of the adventitia of the great vessels some atrophy was noted. Aschoff bodies, or similar pathological lesions, have been reported in cases with pericarditis, but none were seen in any of our cases.

The proportion of cases due to acid-fast infection to those due to other etiologic agents is important when attributing to tuberculosis the major role in producing adhesive pericarditis. About 200 cases of pericarditis have been encountered in the wards of the Hospital for Sick Children in the past 30 years. Only eight of these were due to tuberculosis. They were for the most part rheumatic, bacterial, and

From the wards and laboratories of the Hospital for Sick Children, the I. O. D. E. Hospital for Tuberculous Children, and the University of Toronto Faculty of Medicine, assisted by a Federal Research Grant.

nephrotic. One congenital case was encountered. It would appear, therefore, that the tubercle bacillus is not a common cause of pericarditis in children. It may be commoner in the future, as bactericidal drugs used in the treatment of tuberculosis not only save lives but allow more severe infections to persist longer. This is indicated by the fact that half the tuberculous cases encountered in the past 30 years have occurred in the past 6 years when such therapy was in use.

The pathogenesis of tuberculous pericarditis is almost universally accepted to be due to the infection reaching the pericardium in one of three ways. These are (1) direct extension of the infection from adjacent lymph glands, (2) hematogenous spread (miliary), and (3) by way of the lymphatics. Direct extension from caseous glands is the most common mode of infection. It was the route in all our cases. This fact probably has an important bearing on the treatment of the disease. Dense adhesions surround the glands, great vessels, and pericardial sac. This probably explains the frequency of a dilated vena cava appearing in the roentgenogram. This vessel shadow may be obscured by the massive glandular enlargement.

The only other mode of infection possible would be when the pericarditis is the primary tuberculous infection. This is presumed to be the case when it is the oldest or the sole lesion present. This cause must be extremely rare. Ellman [1] states it may be considered nonexistent. Roubier [2] reported five such cases in 1,300 autopsies. Thompson [3] reported seven cases. These were all of elderly patients. Blatt [4] in 1928, reviewed the literature and failed to find a single reported case of tuberculous pericarditis in a child. There were none in this series.

The symptoms may be precipitated by an injury over the precordium causing hemorrhage or by an intercurrent infection. There is usually some precordial pain. This is not severe, and may be entirely lacking. Tachycardia out of proportion to the fever present is almost constant. Fever is commonly present. In the early cases when the disease pursued its natural course, effusion was always present. Later peripheral edema and general anasarca developed in the early cases, and dyspnea and cyanosis appeared rather late. The large amounts of pericardial fluid aspirated in the early cases were almost incredible. The disease usually ran its course in four to five months.

The signs described as classical in the textbooks, such as polyserositis, dyspnea, cyanosis, and death from heart failure or other tuberculous disease, are those of the disease when its course has not been interrupted by adequate therapy. Fever is variable. Tachycardia is constant. There is a peculiar third sound heard over the precordial area. This is not unlike a presystolic murmur or the sound produced by a gallop rhythm. This third sound was first described in 1856 by Potain.[5] He thought it was produced by calcification of the pericardium. It has been called the proto-

1. Ellman, P.: Tuberculous Pericarditis with Effusion, Brit. Heart J. **7**:147, 1945.

2. Roubier, C., and Dubois (Mme.): La péricardite tuberculeuse primitive du vieillard: Ses formes cliniques, Progr. méd. Paris **40**:1,626, 1930.

3. Thompson, W. P.: Primary Tuberculosis of the Pericardium, J. A. M. A. **100**:642, 1933.

4. Blatt, M. L., and Greengard, J.: Pericarditis as a Primary Clinical Manifestation of Tuberculosis in Childhood, Am. J. Dis. Child. **35**:631, 1928.

5. Potain, P. C.: Adhérence général du péricarde: Triple bruit du coeur; Impulsion diastolique, Bull. Soc. Anat. Paris **31**:378, 1856.

diastolic sound or pleuropericardial snap by McKusick.[6] This author has shown, by recordings of heart sounds and electrokymograms, that the sound is produced by rapid filling of the ventricle in diastole, or by an abrupt halt in ventricular filling. This sound, often wrongly called pericardial friction, lasts as long as two months, in contradistinction to the evanescent type of friction rub heard in rheumatic pericarditis. It has been heard in all but one of our cases (Case 4). According to the literature it is present in 33 to 75% of all cases.

Pericarditis should be suspected when heart failure and an apparently normal heart coexist. In other words, when circulatory failure is present without structural heart disease, pericarditis is a likely cause.

The pulse is rapid and of low tension. The tachycardia has been the symptom suggesting cardiac involvement in two cases.

Peripheral edema was seen in all early cases, but in none of those in which the patient had received antituberculosis drugs.

Pericardial fluid is usually found at some stage of the disease. Like peripheral edema, it is less frequently seen in treated patients. Only one of the treated patients had some fluid, but this was not detected clinically. The fluid in this patient did not show any organisms by culture or guinea-pig inoculation. A number of observers have pointed out the serious significance of positive cultures obtained in pericardial fluid.

Roentgenography has been of little help in the recent cases. Earlier full-blown cases of course presented the classic picture. According to the literature, the roentgenogram presents typical readily recognized features. One feature is the presence of a dilated superior vena cava, especially when this is associated with little or no cardiac enlargement. Under the fluoroscope, there may be complete fixation of the heart and diaphragm. Calcium may be seen. Irregular cardiac borders are sometimes noted.

The electrocardiographic changes are diagnostic, although some of them could be attributed to increases in pulmonary pressure. There is flattening, or inversion, of the T waves in the precordial as well as the limb leads. The curves are low voltage (Barrett[7]). There may be arrythmia. Right ventricular preponderance is frequent; left is less common (Werner[8]). Prolonged conduction time is seen only rarely.

The prognosis of this disease was poor indeed up until the last few years. Children died in five or six months from heart failure or the coexistent tuberculosis. In adults, life lasted longer, often apparently until calcification occurred or greatly constricted cardiac movements resulted from the adhesions present.

The first approach to any treatment other than that giving symptomatic relief, was surgical. Blalock[9] stated the mortality of the disease without pericardiectomy was 100%. In six patients operated on by him, three were cured, two died of miliary

6. McKusick, V.: Chronic Constrictive Pericarditis: Some Clinical and Laboratory Observations, Bull. Johns Hopkins Hosp. **90**:3, 1952.

7. Barrett, A. M., and Cole, L.: Case of Tuberculous Pericarditis, Brit. Heart J. **6**:185, 1944.

8. Werner, G., and Arnold, E.: Observations sur l'électrocardiogramme des tuberculeux pulmonaires, Schweiz. Ztschr. Tuberk. **8**:441, 1951.

9. Blalock, A., and Levy, S. E.: Tuberculous Pericarditis, J. Thoracic. Surg. **7**:132, 1937.

disease, and there was an immediate postoperative death of one. Holman [10] cited five patients treated by operation with three cures and two with marked improvement. Pericardiectomy was advised even in children, and two children treated thus were described by Hantelmann.[11] All those who use the operation advise its early use.

A survey of our cases in which postmortem examination was done appears to indicate, with one possible exception (Case 4), that relief by such operations would not have been obtainable. Even those patients with the thickest pericardium and the most marked constriction had such adhesive changes about the roots of the great vessels, glands, and pericardium that their removal would have been impossible. Their continued presence would have nullified any effect from incising the adherent pericardium lower down.

Antituberculosis drugs would appear to promise more satisfactory therapeutic results. They would accomplish this by the dual action of altering the course of the disease itself and of curing the tuberculous disease elsewhere. Several reports have already been published on the effect of streptomycin in this disease. Myers [12] reported relatively long asymptomatic periods, and death when it occurred was due to coexistent disease elsewhere. Carroll [13] reported a larger series and urged early treatment to avoid the constriction produced by healing, which would invalidate any good results produced.

We have not been too impressed with the direct effects of streptomycin on the pericardial component of the disease in our cases. Any beneficial effects it produced seemed to be on the coexisting disease. One exception might be the patient (C. B., case cited) in whom tubercles seen at the commencement of treatment had disappeared from the pericardium when death occurred two months later. The patient with the most severe constrictive pericarditis (Case 4) had had streptomycin therapy for nearly three months. The organism was sensitive to the drug. Possibly, therapy was started so late that adhesions grew apace before healing could occur. Another patient (D. P.) had had many months of streptomycin therapy, to which the infecting organism early proved insensitive. Her pericarditis occurred after this course of treatment. A third patient (C. B.), with an organism sensitive to streptomycin, had this drug over two months, and aside from the disappearance of the miliary tubercles from the epicardium no effect was apparent.

There are certain inherent defects of streptomycin that would militate against its usefulness in this disease, even with early therapy and a sensitive organism. It is well recognized that it penetrates caseous masses little, if at all, and, further, that whatever small portion penetrates these masses is further inhibited by their acid reaction. One would therefore question its effectiveness in a disease most frequently caused by spread of infection from such masses. Its salutary effects would most likely be on the disease elsewhere, and the benefits achieved due to this.

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10. Holman, E., and Willett, F.: Treatment of Active Tuberculous Pericarditis by Pericardiectomy, J. A. M. A. **146**:1, 1951.

11. Hantlemann, B.: Die Pericarditis calculosa im Kindesalter, Tuberkulosearzt **5**:471, 1951.

12. Myers, T. M., and Hamburger, M.: Tuberculous Pericarditis: Its Treatment with Streptomycin and Some Observations on the Natural History of the Disease, Am. J. Med. **12**:302, 1952.

13. Carroll, D.: Streptomycin in the Treatment of Tuberculous Pericarditis, Bull. Johns Hopkins Hosp. **88**:425, 1951.

We have noticed [14] that isoniazid has more effect on caseous glands. It seemed worth consideration whether it would not prove a better drug than streptomycin in the treatment of tuberculous pericarditis. In the two patients so treated, this possibility would appear likely. When overwhelming tuberculous infection is present elsewhere, streptomycin might quite likely be needed as well.

REPORT OF CASES

Case 1.—M. B., a 6-year-old girl, was poorly nourished and acutely ill when admitted with a history of pain in the abdomen for two weeks and fever for one. There was considerable cardiac embarrassment. The liver was 1½ in. (3.8 cm.) below the costal margin. The spleen was not palpable. The heart sounds were of fair quality. There was a blowing systolic murmur in the mitral area, with a tendency to a presystolic or third sound. The heart was enlarged, the point of maximal impulse being 4½ in. (11.4 cm.) from the midline in the sixth interspace. The temperature rose to 104 F. each day. The tuberculin test was positive, but no organisms were found in the laryngeal swab. Pulmonary tuberculosis was present.

Two weeks later generalized edema and anasarca developed. Dyspnea became more marked. The systolic bruit with a third sound was still present.

After another two weeks, the cough became troublesome. Heart sounds were distant and of poor quality. Pericardial effusion developed, which became progressively worse. The pulse rate was constantly high.

The red blood cell count at this time was 3,400,000, the white blood cell count 16,000, large lymphocytes 10%, hemoglobin 60%. The urine was normal.

Downhill progress was rapid after the development of effusion, and the child died three months after the onset of the illness.

Postmortem Examination.—There were marked general edema and anasarca. All the serous cavities contained much fluid. There were large caseous glands about the right bronchus. The pericardial cavity contained a small amount of straw-coloured fluid. The left ventricle was tightly bound to the pericardium with dense firm fibrous adhesions. There were mural thrombi present. The myocardium was normal. On the pericardial surface was a mass of tissue composed chiefly of proliferating fibroblasts with numerous small capillaries and infiltrated with plasma cells. There were no Aschoff bodies.

Case 2.—H. M., was a 5-year-old girl. The father of the child had tuberculosis. The child had fever for three months before admission. This followed an attack of measles. Abdominal pain had been fairly severe for one month. Cough, loss of weight, and large cervical glands had been noted. The immediate reason for admission was persistent vomiting for three days.

Two tuberculin tests, one a von Pirquet and one intracutaneous, were negative.

The child was emaciated. The heart was not enlarged, and there were no murmurs. Abdominal masses were present. The roentgenogram showed miliary tuberculosis with a very wide mediastinum. The red blood count was 5,750,000, the white blood cell count 16,000, with 75% polymorphonuclear leucocytes. The urine was normal.

The downhill progress was rapid, and death occurred two weeks after admission to hospital.

Postmortem examination showed generalized miliary tuberculosis, with tabes mesenterica and mediastinitis. The pericardium was densely adherent to the heart muscle and covered with numerous tubercles. The heart muscle was normal. There were ragged fibrinous exudate on the pericardial surface and several young tubercles. There was early nephrosis.

Case 3.—C. W., a 22-month-old boy, had cough and difficult breathing for two weeks before admission. There was close contact with several members of the family who had tuberculosis. He died 24 hours after admission. He had generalized miliary tuberculosis with bronchietasis of the right upper lobe and massive mediastinal tuberculosis with an abscess which had ruptured. The pericardium was probably infected by this accident. It was thickened and densely adherent to the myocardium.

14. Boyd, G. L.: Isoniazid in the Treatment of Childhood Tuberculosis, Canad. M. A. J., Sept., 1953, to be published.

Case 4.—J. LeS., a 10-year-old boy, was admitted with far advanced tuberculous meningitis. He had a severe cold seven months previously and a dry hacking cough and fever ever since. Loss of weight had been marked latterly. His meningeal symptoms had been present for three weeks before admission to hospital. He was treated with streptomycin administered intrathecally and intramuscularly and with orally administered thiazolsulfone (Promizole). He lived nearly three months after admission, and, as far as his meningitis was concerned, he appeared to be making progress. His pulse rate was 140 to 160. No clinical signs suggestive of pericarditis were noted. The roentgenogram, even by hindsight, gave no suggestion of pericardial involvement. It was felt that his death could not be explained by his meningitis, but its real cause became apparent at autopsy.

There was no liver nor splenic enlargement. There was marked adhesive pericarditis. It was impossible to separate the two layers of the pericardium. The cavity was obliterated. The areolar tissue around the great vessels was tougher than normal. The heart (including the pericardium) weighed 230 gm. The myocardium showed areas of lymphocytic infiltration. The endocardium was normal. There was a large mass of pink homogeneous material adherent to the pericardium. This consisted of caseating areas and giant cells.

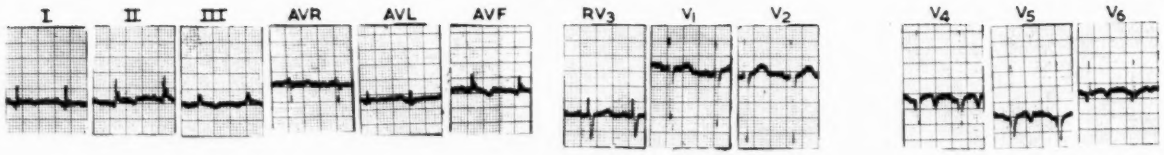
Case 5.—C. B., a 3-year-old boy, was admitted to hospital in November, 1952, with a three months' history of cough and loss of weight. Ten days prior to admission he had been admitted to another hospital, where a diagnosis of tuberculous meningitis was made. He presented the picture of far-advanced generalized tuberculosis and meningitis. His intracranial pressure was so high that immediate burr (prefrontal) holes were done. Before this was accomplished cardiac arrest occurred and respirations soon ceased. The chest was opened and the heart massaged. It was noted that there were tubercles on the pericardium. Respirations started again as soon as the burr holes were made and the intracranial pressure relieved. Despite the advanced stage of the meningitis, his condition improved with administration of streptomycin and *p*-aminosalicylic acid and correction of the profound electrolyte disturbance. Tachycardia persisted and became worse. There was a systolic bruit with an early diastolic murmur at the base. The electrocardiogram showed changes due to pericarditis. Cyanosis developed, and he finally died two months after admission.

Postmortem Examination.—There were no tubercles on the pericardium. The pericardial cavity contained about 30 cc. of clear yellow fluid. At the base of the heart, at the root of the great vessels, the aorta and pulmonary artery were bound together by firm fibrous adhesions which connected with the firm fibrous pericardium, which in turn was connected to the neighboring lymph nodes. It appeared that there had been direct extension of the tuberculous process from the left hilar nodes through the pericardium to the roots of the great vessels. The process healed by fibrosis. The myocardium was normal, but there was a thrombus in the left ventricle.

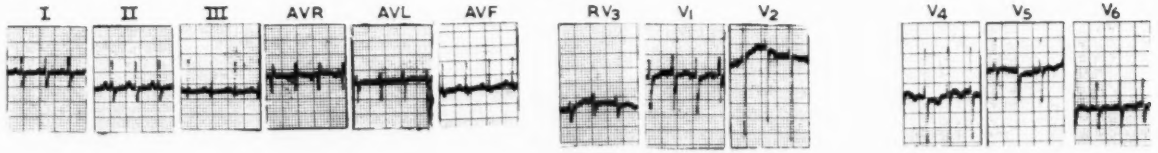
The brain showed still active meningitis.

Case 6.—D. P., was a 7-year-old girl. Her father died of tuberculosis. The child had phlyctenular conjunctivitis before she attended hospital. She first came to the hospital at the age of 5 with far-advanced bilateral caseous pneumonia. The organisms were only slightly sensitive to streptomycin and quickly became completely insensitive. She had an ulcerative constrictive lesion of the left main bronchus, beyond which bronciectasis developed. This became so bad that left pneumonectomy was done two years after admission. She was variously treated with streptomycin, *p*-amino-acid-salicylic acid, viomycin, and thiosemicarbizone, to all of which she made little or no response. Ten months after the lung operation she acquired a sore throat with increased fever. Immediately following this retrosternal pain, slight cyanosis, and tachycardia developed. A murmur developed to the left of the sternum. This had a systolic element, with a third sound. This so-called pericardial friction sound lasted for six weeks. The electrocardiogram shown below was typical of pericarditis. No fluid developed. It was found the infecting tubercle bacillus was slightly sensitive to chloramphemicol (Chloromycetin); this was given for four months and appeared to hold the disease in abeyance. Isoniazid then became available, and the organism proved sensitive to it, so it was given (10 mg. per kilogram of body weight), with the exclusion of other drugs. Her progress on this treatment was rapid and constant in all aspects of her disease, and after nine months' treatment she was allowed up for short periods and a month later discharged home with gradually increasing activity. She continues to be checked at the clinic and to date remains well.

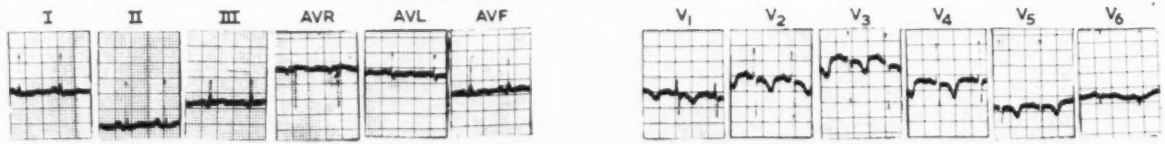
Case VII



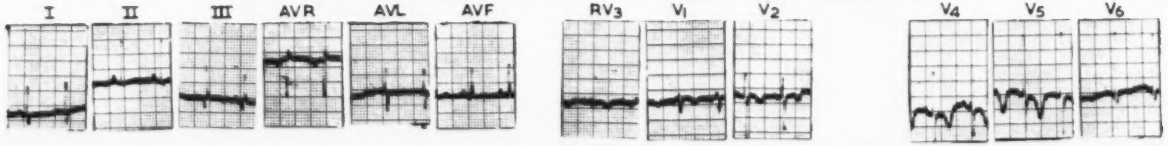
Case V



Case VI... Active Pericarditis



Case VI... Twelve Months after Friction had Disappeared



Electrocardiograms from three cases of tuberculous pericarditis in children.

Case 7.—K. D., a 5-year-old girl, was admitted to hospital first at the age of 11 months, with right middle-lobe tuberculosis. Stomach washings and bronchoscopic suctions were positive for tubercle bacillus on culture and guinea-pig inoculation. She was hospitalized 13 months and treated with bed rest and general care; no specific drugs were given. She was discharged cured. She appeared at the clinic for follow-up examinations at frequent intervals. Eighteen months after discharge she reported at the clinic with no complaints and a report of continued progress. Examination of her previously normal heart revealed a friction rub at the base. There was also a reduplicated second and a third sound, giving an impression of gallop rhythm. An electrocardiogram was done and revealed typical changes of pericarditis. There was no cardiac enlargement. She was again hospitalized and kept at bed rest. She has received isoniazid (10 mg. per kg.) for the past five months. No reactivation of pulmonary disease has been noted. The friction lasted six weeks. Electrocardiographic changes as shown on the chart were typical of pericarditis.

SUMMARY

Observations are made from the study of eight cases of tuberculous pericarditis seen at the Hospital for Sick Children in the past 30 years. The material consisted of clinical material in all and postmortem studies in six of them.

The possible chemotherapeutic benefits to be derived from streptomycin and isoniazid are discussed. The latter promises to be of value.

Progress in Pediatrics

PRESENT STATUS AND FUTURE POSSIBILITIES OF A VACCINE FOR THE CONTROL OF POLIOMYELITIS

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SINCE there is an impression that a practicable vaccine for poliomyelitis is either at hand or immediately around the corner, it may be best to start this discussion with the statement that such a vaccine is not now at hand and that one can only guess as to what is around the corner. The future possibilities of a vaccine for the control of poliomyelitis depend in large measure on what we still must and can learn with the new tools that have become available to poliomyelitis research in the last few years.

The objective is clear: to imitate what nature does for 99 to 99.9% of the population but without incurring the 1 in 100 to 1 in 1,000 risk of paralysis which in many parts of the world is the price for acquiring immunity to poliomyelitis. The knowledge and tools we had only five years ago provided little hope for achievement of this objective. We know that there was more than one immunologic type of poliomyelitis virus, but we did not know whether the number was 2 or 100. We knew that poliomyelitis virus could be inactivated by formalin or other means without losing its antigenicity, but we also knew that with the available sources of virus the amounts that had to be inoculated, and the number of repeated injections that had to be given to achieve even a minimum immune response were too large for practical consideration. Furthermore, with nerve tissue of monkeys as the chief source of virus, not only would there have been insufficient material with which to work but the danger of postvaccinal paralytic accidents loomed almost as large as the danger of paralytic poliomyelitis itself. While there was circumstantial evidence to suggest that strains of poliomyelitis virus of low virulence probably existed in nature, the techniques that we had for recovering poliomyelitis viruses of necessity yielded only the strains with moderate or high pathogenicity for the nervous system.

What, then, is the new information accumulated in the past five years which has changed this hopeless picture and provided a new approach to the search for a safe and practicable immunizing agent for the control of poliomyelitis? First came the demonstration that among more than 200 strains of moderate or high virulence

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recovered in various parts of the world there were only three major immunologic types.[1] These studies also revealed that the Type 1 (Brunhilde-like) strains were most regularly responsible for the major epidemics, while the Type 3 (Leon-like) strains were encountered only irregularly during epidemics. The Type 2 (Lansing-like) strains thus far have not been found to be the cause of a single epidemic, although they have been recovered in sporadic cases of paralytic and nonparalytic poliomyelitis, and the vast majority of adults, the world over, have antibodies for this type of virus. It is clear, then, that a successful vaccine must first of all be capable of producing immunity against the Type 1 poliomyelitis viruses. Immunity against the other two types is, of course, also desirable.

Unquestionably, the most important new developments in the last five years followed the demonstration by Enders, Weller and Robbins [2] that poliomyelitis viruses not only multiply in human embryonic and adult non-nerve tissues in vitro but also produce a cytopathogenic change by which the presence of virus can be recognized without having to resort to animal inoculation. The subsequent demonstration that various non-nerve tissues of monkeys, especially the kidneys, in in vitro cultures provide a medium in which all three immunologic types of poliomyelitis virus can multiply to a level hitherto unobtained in live monkeys opened many new opportunities for studies in this field. It has become possible to investigate not only the immunogenic capacity of relatively purer, more potent, and more plentiful preparations of virus but also the pathogenic spectrum of variants produced by cultivation or recovered directly in tissue cultures from natural sources.

Two additional experimental observations have provided a more hopeful outlook for studies on artificial immunization against poliomyelitis. One is the demonstration by Bodian [3] that the amount of passively introduced antibody required to protect cynomolgus monkeys against paralytic infection by the intramuscular or oral routes is very much smaller than that needed to protect against infection by the nasal or cerebral routes, and the other is based on the studies of Freund [4] indicating that certain adjuvants can enhance the immune response to a variety of antigens, including those of the poliomyelitis viruses. The field trials of Hammon and his associates [5] on the prophylactic effect of small doses of human gamma globulin,

1. Immunologic Classification of Poliomyelitis Viruses: Discussion of Results and General Summary, Committee on Typing of the National Foundation for Infantile Paralysis, Am. J. Hyg. **54**:268, 1951. Also Additional Data to be Published.

2. Enders, J. F.; Weller, T. H., and Robbins, F. C.: Cultivation of the Lansing Strain of Poliomyelitis Virus in Cultures of Various Human Embryonic Tissues, Science **109**:85, 1949. Robbins, F. C.; Weller, T. H., and Enders, J. F.: Studies on the Cultivation of Poliomyelitis Viruses in Tissue Culture: II. The Propagation of the Poliomyelitis Viruses in Roller-Tube Cultures of Various Human Tissues, J. Immunol. **69**:673, 1952.

3. Bodian, D.: Experimental Studies on Passive Immunization Against Poliomyelitis: I. Protection with Human Gamma Globulin Against Intramuscular Inoculation, and Combined Passive and Active Immunization, Am. J. Hyg. **54**:132, 1951; II. The Prophylactic Effect of Human Gamma Globulin on Paralytic Poliomyelitis in Cynomolgus Monkeys after Virus Feeding, Am. J. Hyg. **56**:78, 1952.

4. Freund, J.: The Effect of Paraffin Oil and Mycobacteria on Antibody Formation and Sensitization: A Review, Am. J. Clin. Path. **21**:645, 1951.

5. Hammon, W. M.; Coriell, L. L.; Wehrle, P. F., and Stokes, J., Jr.: Evaluation of Red Cross Gamma Globulin as a Prophylactic Agent for Poliomyelitis: IV. Final Report of Results Based on Clinical Diagnosis, J. A. M. A. **151**:1272, 1953.

if confirmed by future observations, also suggest that the amount of antibody required to protect human beings against the paralytic consequences of poliomyelitis infection may not be very large.

With this new information there are three main approaches to the problem of immunization against poliomyelitis: (1) a "killed" virus vaccine, (2) immunization with active virus under cover of antibody, and (3) an avirulent virus vaccine. The work on "killed" virus vaccines produced with poliomyelitis viruses propagated in tissue cultures is in its infancy. Salk and his associates [6] published an abstract of work on monkeys, in which it was stated that the antigenicity of formalinized tissue culture vaccines, as measured by development of antibody, was comparable to that obtained with similar vaccines prepared from nervous tissue. The work covered by his report was done with tissue cultures of monkey testicles, which yield much less virus than similar cultures of monkey kidney. The basic information that one should have about a vaccine before it is tested in human beings is not yet available. The main issue in such work is concerned with quantitative rather than qualitative questions. The question one asks is not does this experimental vaccine produce antibody but, rather, how much of a given preparation represents a minimal immunogenic dose. The first objective, therefore, for proper orientation is the development of a suitable reproducible method of assay—in experimental animals, not in human beings. With such an assay method one can then determine the best way to inactivate the virus, the best strain of virus to use, the keeping qualities of the vaccines, the best dosage schedule, and, above all, the reproducibility of the results. The infectious titer of a virus preparation before inactivation is not an adequate index to what its antigenic potency will be after inactivation and storage. Tests on human beings can be evaluated properly only in terms of some standard assay value, so that on repetition with another preparation one can tell whether the same amount of antigen is being used, 100 times more, or 100 times less. There are as yet no experimental data to show that monkeys inoculated with "killed" Type 1 poliomyelitis tissue culture vaccine are protected against the paralytic infection by the oral route or, what is even more important, the minimal amount of such a vaccine that is needed to produce antibody or provide such protection and how long such protection persists.

Salk and his associates [7] have recently reported in great detail the results of their first tests with "killed" tissue culture virus vaccines in human beings and concluded that "in one series of experiments it appears that antibody for all three immunologic types was induced by the inoculation of small quantities of such vaccines incorporated in a water-in-oil emulsion." The small quantities used represented only 0.1 ml. of tissue-culture fluid for each of the three types, and if such small amounts of inactivated material could actually produce antibody in human beings who did not already possess it a very practical vaccine would indeed have been at hand. This is not, however, what these investigators have demonstrated as yet. The 16 persons used in this test lived in an institution which experienced a

6. Salk, J. E.; Lewis, L. J.; Bennett, B. L., and Youngner, J. S.: Immunization of Monkeys with Poliomyelitis Viruses Grown in Cultures of Monkey Testicular Tissue, abstracted in Fed. Proc. **11**:480, 1952.

7. Salk, J. E.: Studies in Human Subjects on Active Immunization Against Poliomyelitis: I. A Preliminary Report of Experiments in Progress, J. A. M. A. **151**:1081, 1953.

rather severe outbreak of poliomyelitis late in 1951, and all 15 persons who were tested for development of antibody to Type 1 poliomyelitis virus already had such antibody in titers of 1:16 to 1:2,048 before they received the vaccine. Eleven of the 15 exhibited a fourfold or greater rise in titer. It is well known that it takes very much less antigen to act as a booster than to produce antibody *de novo*. In this same test, however, there were 6 persons (among 12 tested) whose antibody titer for Type 2 poliomyelitis virus was less than 1:4 and another group of 6 (among 16 tested) whose titer for Type 3 virus was less than 1:4 before vaccination, and in both instances 5 of the 6 developed antibody very shortly after the single injection of vaccine. Here, too, it is probable that the antibody response may represent a booster phenomenon. Absence of antibody in a 1:4 dilution of serum tested against 100 doses of virus in testicular cultures does not mean that the person had no antibody, because we have found, as have others, that 100 doses of virus in testicular cultures may actually represent 1,000 to 10,000 doses of virus when tested in kidney-tissue cultures. Furthermore, it has been shown [8] that many patients who are infected with Type 1 poliomyelitis virus develop a small amount of Type 2 neutralizing antibody which may persist for only a few weeks. Such persons may also be regarded as having been sensitized to Type 2 antigen. It is also possible, however, that the Type 2 and Type 3 viruses are better antigens, an observation already made in experimental work on monkeys and chimpanzees and also by Howe [9] in tests on a few children with formalinized nerve-tissue vaccine. While it is important to know that such a small amount of vaccine may act as a booster, it is much more important to find out how much vaccine has to be given to obtain an antibody response to the Type 1 virus in persons who have no demonstrable antibody in undiluted serum to any of the poliomyelitis viruses. This information will no doubt soon be forthcoming, and the results will determine whether or not a vaccine for widespread use can be prepared from monkey tissues or whether some other, more abundant, source of tissue will have to be found.

At this point it may be well to consider some of the requirements for an acceptable "killed" virus vaccine:

1. There must be a plentiful source of tissue in which the virus will grow in high titer.

2. The tissue must not be a potential source of another pathogenic agent which is either more difficult to inactivate than poliomyelitis virus or cannot be detected by simple tests. Hepatitis virus, which is a good example of such an agent, at present presents the chief objection to the use of human tissue. The recent demonstration by Scherer, Syverton, and Gey [10] that a strain of malignant human epithelial cells, which can be grown in large quantities in cultures in vitro, constitutes an excellent medium for propagation of the poliomyelitis viruses has raised the question whether

8. Sabin, A. B.: Transitory Appearance of Type 2 Neutralizing Antibody in Patients Infected with Type 1 Poliomyelitis Virus, J. Exper. Med. **96**:99, 1952.

9. Howe, H. A.: Antibody Response of Chimpanzees and Human Beings to Formalin-Inactivated Trivalent Poliomyelitis Vaccine, Am. J. Hyg. **56**:265, 1952.

10. Scherer, W. F.; Syverton, J. T., and Gey, G. O.: Studies on the Propagation in Vitro of Poliomyelitis Viruses: IV. Viral Multiplication in a Stable Strain of Human Malignant Epithelial Cells (Strain HeLa) Derived from an Epidermoid Carcinoma of the Cervix, J. Exper. Med. **97**:695, 1953.

the fluid from such cultures, freed of cells and formalized, can be used with impunity in human beings. The dilemma here is that, while it is not possible to say yes, it is also not possible to say no, and my own inclination would be not to use such tissue as a source of poliomyelitis vaccine.

3. No strain of poliomyelitis virus which is highly paralytogenic after intramuscular injection should be used. The reason for this is that a minimal amount of such a virus, escaping inactivation by formalin, which may not be detected by intracerebral injection in 10 or 20 monkeys, may yet produce paralysis in 1 of 100 or 1 of 1,000 children. The Type 1 Mahoney virus, used in Salk's preliminary work, is a good example of a virus that should not be used, because in minimal doses it produces paralysis as readily after intramuscular as after intracerebral injection.

4. The vaccine must not in itself be potentially dangerous for various other reasons even to 1 person in 1,000. Since multiple inoculations of any killed virus vaccine will undoubtedly be necessary, special attention will have to be paid to the potential danger of anaphylaxis, organ damage, and the safety of adjuvants that may have to be used. The recent report of Freund and his associates [11] that extracts of testicle inoculated with oily adjuvants and mycobacteria can lead to degeneration of the testicles emphasizes the need of extensive studies with other organ and tissue extracts before they are used with adjuvants on a large scale in human beings. Studies on guinea pigs of the anaphylactogenic capacities of various preparations inoculated with adjuvants are also indicated.

When a "killed" virus vaccine fulfilling all the requirements for antigenic potency, safety, and plentiful source of tissue is found, another very important question that will have to be answered is whether or not, or to what extent, it will interfere with the subclinical infections which under natural conditions immunize the vast majority of the population against poliomyelitis. The immunity imparted by "killed" virus vaccines is ordinarily short, and, while adjuvants may be expected to prolong this period, no one as yet knows for how long. The point is that poliomyelitis is usually a severer disease in older age than in early childhood, and one would like to know whether active immunization with a "killed" virus vaccine would have to be repeated periodically for the rest of a person's life. Experimental observations already at hand indicate that certain levels of antibody do not prevent inapparent infection with large doses of active poliomyelitis virus. The response to small doses, however, may be quite different. Furthermore, under the conditions of viral dissemination obtaining in a country like the United States, where only about 50% of young adults may possess antibodies indicative of past infection, the opportunity for acquiring an active infection may not present itself for many years. The final answer to this question can be obtained only by controlled tests on various population groups in different parts of the world, i. e., in regions where viral dissemination is extensive, as judged by the fact that 90 to 100% become immune during the first three or four years of life, as well as in the United States. This will call for field tests in which the appearance and persistence of antibodies for all three types

11. Freund, J.; Lipton, M. M., and Thompson, G. E.: Aspermatogenesis in the Guinea Pig Induced by Testicular Tissue and Adjuvants, J. Exper. Med. **97**:711, 1953.

of poliomyelitis virus in vaccinated and unvaccinated persons can be followed over a period of at least five years. There are those who maintain that an otherwise practical and effective "killed" virus vaccine which will prevent subclinical infection under natural conditions should not be used on a large scale if it has to be reinjected every two or three years for the rest of a person's life, because it would postpone susceptibility to poliomyelitis to a more dangerous age. On the other hand, it is difficult to counter the argument of those who maintain that a safe and effective "killed" virus vaccine should not be withheld, because before too many years have passed there will either be an avirulent virus vaccine or some way will have been found to implement immunity artificially with a virus of markedly reduced virulence.

Let us now consider what is known at this time about immunization with active virus under cover of antibody. So-called neutral antibody-virus mixtures, injected parenterally, have not been found to produce antibody and are also not without danger, because a small amount of virus may frequently remain unneutralized. Experiments carried out in my laboratory on feeding of neutralized virus mixtures to cynomolgus monkeys indicated that a certain amount of dissociation may occur in the alimentary tract, with the resulting immunization of 20 to 30% of such monkeys ingesting three doses of virus. However, when mixtures containing a large excess of antibody were fed, the number of monkeys developing antibody became negligible. Our conclusion was that this procedure was probably neither practical nor safe. Bodian [3] has shown that when antibody, in the form of human gamma globulin, was injected at one site and active virus was given intramuscularly at another, monkeys developed antibody, but the risk of paralysis was not completely eliminated, since with one strain of virus 3 of the 24 monkeys became paralyzed. Further work, however, is indicated to determine whether strains of markedly reduced virulence may be used with safety under these conditions.

The virulence of poliomyelitis viruses refers to their capacity to produce paralysis, and this property can vary not only with the route of inoculation but also with the host. It is becoming increasingly evident that the capacity to produce infection or paralysis by different routes of inoculation and in different hosts depends on special properties possessed by different virus particles. The ratio between the paralytic titer and the infectious titer of a given strain for a given host and route may well be taken as the index of virulence. Thus a virus of low or reduced virulence would be one with a high infectious and low or negligible paralytic capacity. A virus would be considered as avirulent for a given host and route when it retained the capacity to multiply and produce antibodies but was completely incapable of producing paralysis. On the basis of these definitions there are now available poliomyelitis strains of low or reduced virulence but none has as yet been found or produced which may be called avirulent.

Enders, Weller, and Robbins [12] have reported that the Type 1 (Brunhilde) strain of poliomyelitis virus after serial passage in tissue cultures of human nonnerve tissue lost most, but not all, of its capacity to produce paralysis in intra-

12. Enders, J. F.; Weller, T. H.; and Robbins, F. C.: Alteration in Pathogenicity for Monkeys of Brunhilde Strain of Poliomyelitis Virus Following Cultivation in Human Tissues, Fed. Proc. **11**:467, 1952.

cerebrally inoculated monkeys. Studies which I have carried out together with Winsser and Hennessen have indicated that serial propagation of the highly virulent Y-SK strain of poliomyelitis virus in tissue cultures of cynomolgus kidneys resulted in no modification of its virulence for cynomolgus monkeys by the intracerebral, oral, or subcutaneous routes.[13] If mere cultivation in non-nerve tissue does not yield a variant with reduced virulence for the nervous system of the same host, one cannot be certain that the virus cultivated by Enders and his associates in human non-nerve tissue has lost much of its pathogenicity for the human nervous system. However, it is also possible that these investigators have accidentally picked up a mutant or variant with negligible pathogenicity for the nervous system of both monkeys and man. Would such a mutant produce nonparalytic infection and immunity after feeding or parenteral administration to cynomolgus monkeys? After 17 passages of this virus in human tissues, Dr. Enders sent a large amount of it for study in my laboratory. The virus had a cytopathogenic titer of approximately 10^{-5} per milliliter in human uterine tissue, 10^{-2} in cynomolgus testis, and $10^{-5.7}$ in cynomolgus kidney tissue cultures. On intracerebral inoculation in cynomolgus monkeys paralysis developed in only 1 of 14 receiving 1 ml. of the undiluted culture fluid (approximately 500,000 cynomolgus kidney cytopathogenic doses), although lesions were found in the spinal cord of others; of 30 monkeys inoculated with the 10^{-1} to 10^{-6} dilutions (five monkeys per dilution) paralysis developed in only one which received the 10^{-2} dilution, and lesions were found in only a few of the others. Despite the high cytopathogenic titer of this virus for cynomolgus kidney, no antibodies appeared in 20 cynomolgus monkeys which were fed several large doses of this virus, and they were not immune to challenge with a virulent virus by the oral route. The effect of parenteral injection of this virus is now under investigation. It is obvious that in cynomolgus monkeys this virus of markedly reduced virulence for the nervous system is useless for immunization via the alimentary tract. Whether or not this means that it would also be useless in human beings can only be answered by actual test. Simultaneous tests of this virus in chimpanzees by intracerebral, alimentary, and parenteral routes would also indicate whether or not this more highly developed primate can be more useful than the cynomolgus monkey as an index to the pathogenic spectrum of certain strains of poliomyelitis virus in man. Since we have failed to obtain any significant evidence of infection or immunization by feeding both mouse-passaged and cynomolgus-passaged Lansing virus to cynomolgus monkeys under optimum conditions, and since Howe, Bodian, and Morgan[14] have shown that the same strain of virus produces antibodies when it is fed to chimpanzees, it is not improbable that chimpanzees may prove to be a better indicator for the selection of virus strains that may prove to be useful in man.

The observations of Koprowski and his associates[15] have an important bearing on this question. These investigators showed that the TN strain of Type 2 polio-

13. Additional comments are included in the Addendum, p. 309.

14. Howe, H. A.; Bodian, D., and Morgan, I. M.: Subclinical Poliomyelitis in the Chimpanzee and Its Relation to Alimentary Reinfection, Am. J. Hyg. **51**:85, 1950.

15. Koprowski, H.; Jervis, G. A., and Norton, T. W.: Immune Responses in Human Volunteers upon Oral Administration of a Rodent-Adapted Strain of Poliomyelitis Virus, Am. J. Hyg. **55**:108, 1952. Koprowski, H.; Jervis, G. A.; Norton, T. W., and Nelsen, D. J.: Further Studies on Oral Administration of Living Poliomyelitis Virus to Human Subjects, Proc. Soc. Exper. Biol. & Med. **82**:277, 1953.

myelitis virus, which after passage through cotton rats lost much of its virulence on intracerebral injection in monkeys, produced antibodies in high titer after the feeding of a single dose to two large groups of children. Kőprowski has informed me that recent tests indicated that the same preparation of virus which was effective in the children and chimpanzees failed to produce antibodies when it was fed in large amounts to cynomolgus monkeys. The adaptation of another Type 2 poliomyelitis strain (MEF1) to chick embryos by Cabasso and his associates[16] represents another important advance in the search for variants that may ultimately be used for human vaccination. This chick-embryo-adapted virus has lost much, but not yet all, of its virulence for the nervous system of monkeys, and it is noteworthy that in a limited number of tests it produced antibody after intramuscular injection in the chimpanzee but not in the monkey. The latest and highly significant arrival in the field of poliomyelitis variants is a mouse-adapted strain of Type 1 poliomyelitis virus (Mahoney strain) recently reported by Li and Schaeffer.[17] The remarkable speed with which this virus lost most, if not all, of its virulence for the nervous system of the monkey is most unique, and further observations on its pathogenic spectrum will be of the greatest interest.

It is evident from what has just been said that no completely avirulent strain of poliomyelitis virus that could be used for human vaccination is as yet available. Only future work will show whether or not such strains can be developed in the laboratory and whether loss of virulence for the nervous system of the monkey also means loss of virulence for the nervous system of the chimpanzee and man. Until we have learned a good deal more about the pathogenic spectrum of the many naturally occurring and artificially developed strains of poliomyelitis virus, it may be useless to speculate on whether or not a virus with only slight residual virulence for the nervous system of monkeys should be considered for immunization of man.

Although a certain amount of antigenic overlapping among the three immunologic types of poliomyelitis virus has been revealed by both complement fixation and neutralization tests, there is no evidence that active infection with one type will provide immunity to the others. It has been repeatedly found that in patients with high titers of antibody for Type 2 virus paralytic poliomyelitis due to Type 1 develops.[18] In our laboratory we have found that previous oral infection of cynomolgus monkeys with Type 2 virus provided no immunity to paralysis resulting from ingestion of Type 1 virus. An avirulent virus vaccine will, therefore, have to contain all three types, unless some new strain of unusually broad antigenic composition is found.

The search for avirulent strains of poliomyelitis should stimulate many interesting explorations. In the laboratory, continued propagation in unusual hosts and tissues with ultimate attempts at purification of the different clones of virus particles

16. Cabasso, V. J.; Stebbins, M. R.; Dutcher, R. M.; Moyer, A. W., and Cox, H. R.: Poliomyelitis: III. Propagation of MEF1 Strain of Poliomyelitis Virus in Developing Chick Embryo by Allantoic Cavity Inoculation, Proc. Soc. Exper. Biol. & Med. **81**:525, 1952.

17. Li, C. P., and Schaeffer, M.: Adaptation of Type I Poliomyelitis Virus to Mice, Proc. Soc. Exper. Biol. & Med. **82**:477, 1953.

18. Steigman, A. J., and Sabin, A. B.: Antibody Response of Patients with Poliomyelitis to Virus Recovered from Their Own Alimentary Tract, J. Exper. Med. **90**:349, 1949.

may perhaps be most rewarding. In the field, we must search for avirulent strains not only among human beings during interepidemic periods, but we must also not overlook the possibility of the existence of close antigenic relatives in the animal kingdom. During the past year Fieldsteel and I have found neutralizing substances for all three types of poliomyelitis virus in the sera of adult cows. Winsser and I have been unable to infect calves, devoid of such antibody, with virulent poliomyelitis virus. The neutralizing substances which are usually present in low titer have all the properties of human antibody and are precipitated with the globulin fraction. Available data strongly suggest that cattle, and possibly also other animals, may be infected with an agent or agents antigenically related to the three types of human poliomyelitis virus, and the search for such an agent should be part of the over-all attack on this problem.

SUMMARY

Although there is as yet no practicable vaccine for the control of poliomyelitis, the new techniques which have become available in the last few years make it possible to attack this problem with more vigor and greater resources than ever before. All three approaches to vaccination, namely, by "killed" virus, by active virus of low virulence under cover of antibody, and by the search for completely avirulent strains, should receive extensive and simultaneous investigation, because one cannot know from which direction the answer will come. Unquestionably the ultimate goal for the prevention of poliomyelitis is immunization with "living" avirulent virus which will confer immunity for many years or for life. In my opinion, more investigators are now needed in the field of poliomyelitis than ever before, because it is more correct to say that we have only just begun to learn than to create the impression that the job is nearly finished.

ADDENDUM

Since this paper was prepared for presentation, additional observations have been made in my laboratory on the pathogenic and immunogenic spectrum of poliomyelitis viruses propagated in different ways in cultures of non-nervous tissues. Thus, it was found with both Type 1 (Mahoney strain) and Type 2 (Y-SK strain) poliomyelitis viruses that when very large numbers of virus particles were used to initiate multiplication in cynomolgus kidney tissue cultures and serial passages were made very rapidly there appeared variants or mutants with markedly diminished virulence for the nervous system of cynomolgus monkeys and a markedly enhanced level of multiplication in kidney tissue culture. Quantitative determinations of the various types of activity have shown that these cultures are mixtures of very large numbers of "nonparalytogenic" particles (as high as 100,000,000 per milliliter and very much smaller numbers of the original virulent particles, and it should be possible to separate the two by the terminal dilution technique. This is in marked contrast to the perpetuation of virulence for the nervous system which occurred when single or small numbers of virus particles of the same strains were continuously used to initiate multiplication, as was reported in the body of the paper.

Further studies on the Type 1 (Brunhilde) strain of virus, originally propagated in human tissue by Enders, Weller, and Robbins, revealed that, while it was not immunogenic in cynomolgus monkeys when administered by the oral or intramuscular routes, it did produce immunity without paralysis when it was given to

chimpanzees by these routes. Furthermore, even intracerebral injection of this virus in chimpanzees failed to produce paralysis or any other signs of disease. After 12 rapid passages of this virus in cynomolgus kidney cultures with large inocula, it retained its "avirulent" character in the sense that paralysis developed in only an occasional monkey after intracerebral injection and passage from the paralyzed animal to others was negative. Of special importance to the ultimate characterization or definition of an "avirulent" strain of poliomyelitis virus is our recent finding that very large doses of certain variants (as determined by cytopathogenic titer in tissue culture) upon direct intracerebral injection may produce paralysis in an occasional monkey without giving rise to transmissible virulent virus. These observations, as well as other studies now in progress, greatly increase the probability that avirulent poliomyelitis viruses will become available for active immunization of man.

EPIDEMIOLOGICAL ASPECTS OF GAMMA GLOBULIN PROPHYLAXIS IN POLIOMYELITIS

A Critical Evaluation

JOSEPH A. BELL, M.D.
BETHESDA, MD.

THE PRESENT article was prepared at the request of the American Medical Association as part of the symposium on poliomyelitis. It represents the author's evaluation of published and unpublished data pertinent to the prophylactic use of gamma globulin in prevention of poliomyelitis. The chief sources of data are the four recently published papers of Dr. Hammon and his associates.[1] The critical analyses and opinions of Dr. Alexander Langmuir, Dr. William Clark, Dr. Albert Sabin,[2] Dr. Karl Habel,[3] Dr. Harry Weaver, and others have been obtained through personal communication and carefully considered prior to preparing this discussion.

Inasmuch as many and varied hypotheses have been advanced concerning the epidemiology of poliomyelitis, it is first necessary to summarize very briefly the generally held epidemiologic concept of the natural occurrence of poliomyelitis, so as to bring our thinking onto common ground. Since the paralytic disease is of primary concern, it is also necessary to summarize the attributes reported to influence whether or not paralysis develops in an infected person. From these premises, the gamma globulin prophylaxis of poliomyelitis may be evaluated.

There exist three known immunologic types of poliomyelitis virus that cause paralytic disease. Human infection with one of these types apparently gives substantial and lasting protection against disease due to that type, but possibly no protection against disease caused by the other types. So far as is known, human beings are the only natural hosts of poliomyelitis viruses. In nature, these viruses have been found to grow only in living human cells and are propagated by successive

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2. Sabin, A. B.: To be published.

3. Habel, K.: To be published.

passage from one person to another, usually through direct and possibly indirect human association. These viruses commonly infect the human host without apparent ill effect, except in the comparatively infrequent instances when such infection causes paralysis. It is estimated that this happens only once out of every 100 or more infections or, perhaps, 1,000 or more infections and reinfections. Thus, in the dynamics of human life, new susceptibles are born every year, with perhaps a few months' passive immunity if born of immune mothers. Gradually, throughout early life, they become infected with the various types of poliomyelitis virus, and by the time they are adults, most of them are immune, even though paralysis has developed in only a few. If one accepts this natural history of infection and disease and appreciates the present futility of preventing human infection, then one looks for control procedures that will assist and enhance the excellent job already being done by nature. We look for a method of preventing the paralytic disease which does not interfere with the mass immunizations which occur naturally every year by apparently harmless infections and reinfections.

With this concept, the most cogent questions about poliomyelitis are as to why infection produces paralysis in a few persons, why the same infection occasionally produces a mild inconsequential illness in others, and why the same infection commonly produces immunity but no apparent illness in the vast majority of other persons. Although some types of poliomyelitis virus may produce a higher proportion of paralytic cases than other types, the above phenomenon apparently occurs with all known types of virus in all parts of the world, year after year, both endemically and epidemically. Thus, it must be due to differences in dosage or in routes of invasion or due to differences in the human host such as the existence of specific antibodies, the speed of antibody response, or other factors. Epidemiologically, we have been unable to identify differences in dosage and routes of virus invasion in the naturally infected human host, hence we have no information on these factors. We do have many observations on human host factors, particularly specific antibodies, but first let us review some general observations.

Pregnant women appear to be more susceptible to the paralytic disease than other women. Also, children who overexert themselves, particularly during the early febrile stage of poliomyelitis, appear to be more prone to have paralysis. There is also evidence suggesting that the paralytic disease is more likely to develop in presumably infected persons if, during the one to three weeks prior to onset, they have experienced a nose-and-throat operation, particularly a tonsillectomy, or an injection of an immunizing agent, such as diphtheria or tetanus toxoid, pertussis vaccine, or possibly an injection of a variety of medicaments. Even assuming that this is true, the apparent influence of these factors is so small that they could not possibly account for any substantial portion of the paralytic cases that occur every year. Their possible influence is so small that it has been demonstrated only in large epidemics, and so small that no one has been able to determine whether the apparent relation is due to these attributes themselves or due to differences in susceptibility—immunity or case reporting or differences in exposure as might occur in attending a clinic. All in all, the evidence suggesting that these factors may predispose to paralytic disease has all been gained in retrospective analyses of associated past events which preclude completely satisfactory controls. Thus, even though there is no direct,

airtight, and completely satisfactory scientific proof that any of these factors predispose infected persons to paralytic disease, there is little evidence to the contrary, and we cannot ignore the associated facts.

It is here pertinent to digress from the main theme and recount the practical effect of the above information gained in the progress of medical science. In this country, parents fear poliomyelitis, and everything new is widely advertised in the lay press. Thus, during the summer season, reports of poliomyelitis hit the front page; many children are denied the benefits of camps and swimming, and vacation plans are altered even though the risk of travel may be far greater than the risk of paralytic poliomyelitis. Wherever an epidemic exists, physicians postpone tonsillectomies and immunizations which can, with reasonable safety, wait until the end of the epidemic. All this is done because we like to do every little thing that might possibly decrease the risk to an individual child, even though it has not been absolutely proved beyond doubt that the possible decreased risk outweighs the inconvenience and benefits of normal activities.

We have discussed general factors apparently associated with development of paralytic disease; now let us consider the existence of antibodies and prevention of paralytic disease. When infection is introduced into small isolated communities where it has not been present for many years, older age groups appear just as prone to acquire the paralytic disease as younger children. In large nonisolated communities where poliomyelitis viruses have had wide dissemination for many years, the older age groups are not prone to acquire paralysis when exposed to infection. Adults from such large communities are more likely to have demonstrable specific antibodies in their blood than children, who in turn are more prone to paralytic disease. Infants exposed to infection are not prone to acquire the paralytic disease, and this is presumably due to the passive antibodies acquired from their mothers. The gamma globulin obtained from a large pool of adult human blood collected in the United States has been shown to contain specific antibodies against all three types of virus. Injection of this gamma globulin into animals prior to challenge with the infectious virus will prevent the development of paralysis. All in all, there is considerable evidence indicating that the existence of specific antibodies will prevent the paralytic disease in persons exposed to infection.

In 1951, Dr. Hammon and his associates initiated studies to determine whether injections of small amounts of gamma globulin obtained from large pools of adult human blood would prevent paralytic disease in naturally infected children. They perhaps reasoned that since the virus so commonly lives with the human host without apparent harm, a small amount of passive antibody, possibly too small to be detected by present laboratory procedures, might shift the balance from paralytic disease to harmless infection.

By reviewing these specific studies we can see wherein the results may be projected to general use. They selected for study children of the most susceptible ages in three sizeable communities where large epidemics of poliomyelitis were in progress. An attempt was made to give gamma globulin to study children at the time of greatest risk of infection, that is, near the peak of the epidemic. The test group received 0.14 cc. of gamma globulin per pound (0.5 kg.) of body weight intramuscularly in the buttock, and the control group received a similar injection

of an equivalent amount of apparently harmless gelatin. The subsequent observations of these children were comparable, as no one knew who received what until all data were collected.

The Table is a summary of the number of cases of paralytic poliomyelitis in the test and control group by week after inoculation of each child. There was no significant difference in the number of cases which occurred in the test and control groups either during the 1st week or during the 6th to 13th week after inoculation. On the other hand, during the second to fifth week in both the Iowa-Nebraska and in the total of the Utah and Texas experience, there were definitely fewer cases in the gamma globulin group than in the gelatin group. The excellent study methods used force the conclusion that this difference in number of cases was due to the different substances injected. It must be due either to gamma globulin protection

Number of Cases of Paralytic Poliomyelitis in Test and Control Group by Week After Inoculation of Each Child

(From Published Data by Hammon and Co-workers [1])

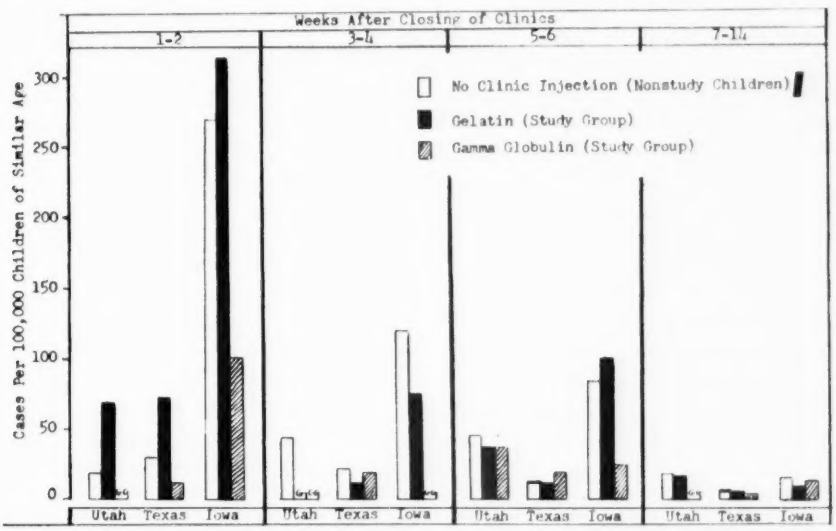
Wk. After Inoculation	Utah and Texas, 19,428 Persons Each Group			Iowa-Nebraska, 7,934 Persons Each Group			Total, 27,362 Persons Each Group		
	G. G.*	Gel.†		G. G.*	Gel.†		G. G.*	Gel.†	
1	4	4		8	12		12	16	
2	1	8		2	16		3	24	
3	2	4	15	1	4	24	3	8	39
4	1	2		0	2		1	4	
5	0	1		0	2		0	3	
6	3	1		0	3		3	4	
7	1	1		2	5		3	6	
8	0	2		1	1		1	3	
9-13	2	3		3	2		5	5	
Total	14	26		17	47		31	73	

* Gamma globulin.
† Gelatin.

in that group, or to an increased incidence in the gelatin group, as considered by Dr. Hammon and associates, or to both.

The big difference between the test and the control group occurred during the second week, as might be expected in any artificial passive immunity which when given during the late incubation period offers no protection. The bulk of inoculations in these three studies was done close to the peak week of the epidemic, and we do not know what would have been the subsequent course had the studies not been done. It is noteworthy that in the gelatin group there is a small but consistent increase of questionable significance 7 to 14 days following clinic attendance. This somewhat parallels the data previously mentioned which show a 7- to 21-day time relationship between certain vaccine injections and the occurrence of poliomyelitis in presumably infected children. However, unlike such data of others, these studies showed no increase in the 14- to 21-day period and no localization of paralysis in the inoculated extremity. Dr. Hammon and associates emphasize the latter, but it has been difficult to demonstrate localization of paralysis following lower-extremity inoculations, and there is reason to question whether the lack of localization has any direct bearing on possible increased incidence.

Obviously, the answer as to whether the difference was due to a decrease in the globulin-treated group or an increase in the gelatin-treated group must come from a strictly comparable control group of noninoculated children of the same age who did not attend the clinics or receive injections. Such a noninoculated group was not included in these studies because the authors felt they would not be adequate for controls. However, the chart shows the biweekly incidence of paralytic poliomyelitis during the 14 weeks following the closing of the clinics in the test and control group, together with the reported incidence in other noninoculated children of the same age in the same community. Data from the latter group are not strictly comparable, but represent the best available. During the first two weeks in each of the three communities, the incidence was higher in the gelatin group than in the non-



Biweekly incidence of paralytic poliomyelitis (prepared from data collected by Dr. Hammon and co-workers[1]).

inoculated group. If this were due to incomplete reporting in the noninoculated group, then one would expect it to be manifest during later weeks, but it was not. This is consistent with a possible but temporary slight increased incidence in the gelatin group, but it is based on extremely few cases and not numerically significant. One might similarly look at the third-fourth week and say that the gelatin gave protection. Much more striking and definite is the gamma globulin group, which shows a significantly lower incidence than either the noninoculated or the gelatin groups. Since the study did not include a strictly comparable group of noninoculated children, we cannot say with absolute scientific finality that the gamma globulin definitely gave protection, but taking all facts into consideration, the overwhelming balance of evidence indicates that the gamma globulin given under these particular circumstances induced a temporary immunity to paralytic poliomyelitis in some, but not all, children.

Since the incubation period is generally 7 to 14 days, the one-week delay in response, noted in the Table, may be due, logically as in measles, to ineffectiveness of gamma globulin protection when given late in the incubation period. It has long been recognized that the administration of convalescent blood after the onset of poliomyelitis does not modify the course of the disease. The 12 cases occurring in less than one week following gamma globulin injection were presumably in those inoculated during the late incubation period and are reported to be less severe than the 16 cases in the gelatin group. I feel that the reported modification in these few cases was definite, but so slight as to warrant no practical consideration unless confirmed by study of a large group of cases. It is noteworthy that the few cases occurring two to five weeks after the children were given gamma globulin were apparently not modified.

To project this experience to the general use of gamma globulin, we must estimate the amount of protection, even though it is risky to extrapolate from so few cases. Let us assume that all the difference in the number of cases in the test and control groups represents cases prevented, ignoring the unproved but possible artificial factors involved. The Table shows that in the Iowa-Nebraska study this difference in the two- to five-week period was 21 cases, or in the total, 30 cases out of some 8,000 inoculations, making a protection rate of 26 to 38 cases per 10,000 children inoculated. In this experience, children aged 1 to 11 were all inoculated during one week very close to the peak of a tremendous epidemic; the paralytic attack rate was 358 per 100,000 persons of all ages during the study year, and almost 1 per 100 in the age group studied. Such an opportunity for general use of gamma globulin in sizeable population groups seldom occurs; thus, this study experience is hardly applicable to general use. So let us look at the Utah and Texas experiences which included large, but not tremendous, epidemics. The inoculations were given to even more limited age groups during a brief period after the peak of the epidemic, but still during a period of high prevalence. Here the protection rate was only about one-fifth that of the Iowa-Nebraska study, that is, only five to six cases prevented out of 10,000 children inoculated. It would appear that this latter experience more closely parallels what might be expected in general use of gamma globulin, but, in general use the protection rate will probably be much less because less-susceptible older children will probably be inoculated and because the inoculations will not all be given at the period of greatest risk, i. e., near the peak of the epidemic when the prevalence is high. Thus, except in tremendous epidemics, the mass use of gamma globulin in children of a community does not offer much hope of preventing a substantial proportion of paralytic cases. However, it is conceivable that its mass public-health use under very special and localized circumstances might possibly precipitate an early decline in the epidemic, but this would be very difficult to establish.

Since the data indicate protection from paralytic disease when gamma globulin is given just prior to infection or perhaps during the very early incubation period, let us examine other possible general uses of gamma globulin. During large epidemics, it might be used in pregnant women and in persons requiring tonsillectomies, as such persons apparently experience a greater risk of paralytic disease. Experience with animals suggests that large doses may be necessary for protection of the latter. We have no experience with humans from which to make a guess as to the value of its use in such circumstances.

From past human experience, we know that persons living in a household with a person having a definite case are more prone to acquire paralytic disease than other persons. The secondary household-attack rate varies with age, perhaps from 2% to 3% at the younger age to 1% for all ages. It is estimated that three to five or more days would generally elapse between day of onset of initial household case and the time when gamma globulin inoculation of other household siblings could be accomplished. In addition, about seven more days would elapse without appreciable protection because the inoculation could have little protective effect when given during the late incubation period. This makes a total of 10 to 12 days, but unfortunately, some 90% of all persons who will get the disease from household contact will have onset before that time. Thus in general use of gamma globulin in household contacts, there remain only 1 to 3 persons out of every 1,000 household contacts of definite cases who could possibly be protected by the inoculation. It is pertinent to realize that persons exposed in a household may experience more continuous and prolonged exposure to perhaps larger doses of infection than is generally experienced outside the household. The reported studies do not identify household contacts; thus we have absolutely no data to show how many, if any, cases might be prevented by general use of gamma globulin in household contacts. Such use might reasonably be expected to prevent a few cases, but since as many as 95% of households may not have secondary cases, and since so few of the remainder could be protected, this general use of gamma globulin cannot be expected to prevent a substantial proportion of the total paralytic cases that occur. However, household contacts can be readily identified and do represent known exposures.

With the above summary of facts and deductions, it is pertinent to point out a few of the unknown. As yet, there are no published data on the quantity of antibodies against each of the three immunologic types of poliomyelitis which were contained in the various lots of gamma globulin used in these studies, and we don't know the variable amount of these antibodies that may be present in the many lots to be used this summer. We don't know the type of virus predominantly responsible for the three epidemics studied, and we don't know the types which will be prevalent in a particular community this summer. We don't know whether larger doses of gamma globulin would have been better, or whether smaller doses would have been adequate. More important, we don't know whether gamma globulin interfered with nature's excellent method of immunizing these children. Dr. Hammon and associates arranged their studies to answer some of these questions, and we must wait until their laboratory studies are completed for the information desired.

In summary, it must be emphasized that the excellent studies carried out by Dr. Hammon and his associates were not primarily designed to determine the effectiveness of the general use of gamma globulin for poliomyelitis prophylaxis. They were obviously arranged to determine whether small amounts of passive antibody could possibly, under the most optimum conditions, prevent the paralytic disease in humans. These studies give the answer for which they were specifically designed, and this is an important contribution to medical science. The procedures used to obtain this answer required the selection of the three most susceptible and highly exposed groups of children that could be found in the United States in areas suitable for study. It is difficult and hazardous to project these results, based on perhaps less than 40 critical cases, to the results that might be expected in the general

widespread use of millions of doses of gamma globulin having an unknown amount of specific antibody to virus Types 1, 2, and 3 and used in different epidemics in different areas and in groups of persons perhaps neither so susceptible nor exposed in a manner similar to those observed in the study.

In conclusion, the present article was prepared in an effort to help the doctor carry out his responsibilities to his patients. The individual parent is more concerned about his child than about medical statistics, but it behooves the physician to know that even though a gamma globulin injection of 0.14 cc. per pound of body weight is apparently harmless when properly given, it appears that in general widespread use, only one child out of many thousands inoculated will be prevented from getting paralytic poliomyelitis. Of course, this chance will vary tremendously depending upon whether that child has just been or immediately will be infected. The benefit during the first week following inoculation would be extremely slight; during the second week it would be at the maximum, but still not 100%; thereafter, the benefit would rapidly decrease so as to be practically nonexistent by the sixth week. Even if you should find not a single case following 1,000 or, perhaps, even 10,000 injections, this does not in itself necessarily mean that any cases were prevented. On the other hand, even if you find a case developing in a person following injection, remember that such cases also occurred in the study group. It might also be pertinent to remember that at least 1 pint (473 ml.) of whole human blood must be collected and processed to produce the one dose of gamma globulin recommended for poliomyelitis prophylaxis in one 50-lb. (22,680 gm.) child.

In spite of the above facts and deductions, gamma globulin remains the only specific prophylactic agent available this year for human poliomyelitis. We all wish we had a crystal ball which would tell us in advance exactly who is destined to get paralytic poliomyelitis so that we might give him gamma globulin one to three weeks before onset. Since we don't know this, its practical application in general use will involve thousands upon thousands of useless injections with the hope of preventing the dread paralytic disease in comparatively rare instances. Nevertheless, we shall all do the best we can under the circumstances this summer.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

Dr. Irvine McQuarrie, M.D., President

SIXTY-THIRD ANNUAL MEETING

Atlantic City, N. J., May 6, 7, and 8, 1953

Postmaturity Clinical Syndrome and Pathologic Findings. Dr. Stewart H. Clifford, Boston.

At a meeting of the American Pediatric Society in 1944, the author reported that 20% of infants with yellow-stained vernix, skin, nails, and umbilical cords were postmature. Taylor, James, and Henserson, of Edinburgh, have recently confirmed our findings. Before this same group in 1951, Clifford, Reid, and Worcester demonstrated that postmaturity, defined on the basis of gestational age, ranked second only to prematurity as a cause of fetal and neonatal mortality. The present communication describes the findings encountered in 37 live-born infants on whom the clinical diagnosis of postmaturity was made at birth.

Two progressive physiologic changes occurring in utero are believed to explain the clinical findings that have been observed in postmature infants. These are the maceration of the skin secondary to the disappearance of the protective layer of vernix caseosa and the degeneration of the placenta occurring as a result of the aging process.

The clinical findings observed in postmature infants can be divided into three groups, depending on the stage of postmaturity encountered. In postmaturity of the first degree, the skin shows the effects of loss of vernix being described as dry, cracked, parchment-like, or peeling, but is unstained by meconium. The infant as a whole reflects the failure of the placenta to provide normal nutrition, with the infants being relatively long and thin and showing evidence of having lost weight recently in utero. Most of these babies appear to be much older than the usual newborn babies, and are open-eyed and alert. Thirteen infants were in this group with no deaths. Three had symptoms of intracranial pathology believed to be the result of intrauterine anoxia, a severe secondary skin infection diagnosed as Ritter's disease developed in one. The percentile distribution of their gestational ages was 10%, 285 days; 50%, 287 days, and 90%, 309 days.

The second stage of postmaturity is characterized by all the changes already recorded to a more marked degree but in addition signs of severe placental degeneration producing anoxia and the liberation of meconium. The amniotic fluid, placental membranes, umbilical cord, and skin are all stained green. There were 11 infants in this group, with four deaths (36% mortality). Severe fetal distress during labor was noted in five, seven were markedly asphyxiated at birth. Six infants showed the hyaline-membrane syndrome and one, intracranial symptoms. The percentile distribution of their gestational ages was 10%, 290 days; 50%, 295 days, and 90%, 300 days.

The third stage of postmaturity is a continuation of the second, but with the passing of time the skin, nails, and cord now are stained a marked yellow color. There were 13 infants in this group, with two deaths (15% mortality). Intrauterine fetal distress had been noted in two, and six babies were severely asphyxiated at birth. Six showed the hyaline-membrane syndrome, one of these accompanied by severe intracranial symptoms. The percentile distribution of their gestational ages was 10%, 291 days; 50%, 302 days, and 90%, 324 days.

Whatever the stage of postmaturity, almost every baby at birth appeared relatively long and thin and poorly nourished; at times the flabby skin hung in folds suggesting an advanced celiac syndrome. All gained at an abnormally fast rate and during this period were difficult to manage due to excessive crying and demands for food.

The pathologic findings were all those associated with intrauterine anoxia. The most frequent findings were in the lungs, where evidence of aspiration of amniotic fluid, meconium, squamous cells, and amorphous debris was an almost universal finding. The atelectatic areas were usually

of patchy distribution, and the bronchi were frequently filled with epithelial cells. Hyaline membranes were occasionally encountered, but only as incidental findings and secondary in importance to the aspirated material. Areas of emphysema involving the lungs and mediastinum were frequent.

Various degrees of postmaturity can be recognized easily at the initial examination of the newborn infant. The more advanced stages of postmaturity carry high morbidity and mortality rates.

DISCUSSION

DR. MYRON E. WEGMAN, Washington, D. C.: I think Dr. Clifford's repeated drawing of our attention to this problem is a most commendable and important effort. The numbers of children involved here are significant in part because we have much greater opportunity, from the standpoint of time, to do something in prevention.

At the meeting, two years ago, when we discussed this question previously, we went over some of the problems involved in prevention and the lack of our knowledge about it. I should like to call attention to one thing that bothers me in the data presented here. In our own statistical studies of this same problem, we found that the mortality rates became higher the farther we departed from the mean birth weight. We, however, used birth weight as an index of postmaturity, rather than time, i. e., gestational age, as Dr. Clifford has used here. I don't quite understand why in his experience the more postmature children, that is, those farthest from the average gestational age, apparently have a higher mortality rate. This may be a sampling error because of the small numbers, but Dr. Clifford may have another explanation.

DR. BELA SCHICK, New York: I have been interested in this problem for many years; I congratulate Dr. Clifford for his excellent presentation. There cannot be much added; it is a magnificent description of all symptoms.

But I am also interested in another part of overmaturity—I prefer to call it overmaturity instead of postmaturity. Not all these children are damaged and have greater mortality or greater morbidity, but there are children that are benefited by too long a gestation.

I am particularly intereted in these children, and I must say I am very much impressed with how well these children look. The skin is white like the skin of an older infant. The child has no icterus at all. He is very alert and opens his eyes and looks around as if he were interested in what he sees. The intrauterine life, is a kind of Shangri-La where the child finds himself in a very nice environment, and as long as the placenta functions satisfactorily it is not always bad.

I think it would be interesting to follow these children. In former years in Vienna, where we had a very strict indication for Caesarean section, we more frequently had overmature children, and I could make the diagnosis of an overmature child in the nursery very easily. We found that to count the gestation period is very difficult and not very reliable. Overmaturity is better judged by the size of the child. For instance, I lately saw a child 57 cm. in length and beautiful looking. Some of the overmature children laugh at 10 to 14 days of age. I don't expect the child to walk earlier, but certain things will be very interesting to follow up, for instance, the mental development.

Some animals run around immediately after birth, such as the guinea pig, and eat immediately the full diet. This we cannot expect in human babies.

I would be interested in knowing whether Dr. Clifford has followed up the overmature babies.

DR. IRVINE MCQUARRIE, Minneapolis: What sort of children are they later? Have you been able to follow them? Are they mentally a little superior?

DR. STEWART H. CLIFFORD, Boston: Our statistics show that 85% of the postmature deaths occur in utero—for every single liveborn postmature infant who dies, five babies have been stillborn. To answer Dr. Wegman, all of the infants here reported were liveborn, since the diagnosis of postmaturity was made exclusively on clinical findings, usually without foreknowledge of gestational age or birth weight. If stillbirths and neonatal deaths are combined, the result is as Dr. Wegman states, that mortality rises with advancing gestational age. In our cases the mortality for Stage 3 was lower because those experiencing the acute asphyxia of Stage 2 undelivered in utero died in utero if severe, and only the babies in the relatively milder cases survived to be liveborn in Stage 3.

I am not too happy about the term "postmature." I have tried to stress that we are concerned with placental physiology. As used, the term implies that the placenta having reached maturity is now degenerating, and as a result of this process the fetus may be seriously injured. As in all growth, the onset of aging is variable and does not start at a set time. We have seen a number of babies who show signs of "postmaturity" long before maturity as measured by gestational age is reached. On the other hand, we have seen many babies of long gestational age who are in excellent condition, and we assume their placentas were of a type that would undergo late retrogression. Therefore, I am particularly happy about Dr. Schick's remarks about the "overmature" infant; fortunately, there are many more in this category than in the pathologic group I have been discussing. I have no idea how long these overripe babies maintain their apparent superiority. To answer Dr. McQuarrie, I do not know the eventual physical and mental status of these children.

The Changing Respiratory Patterns in Newborn Infants. Dr. Herbert C. Miller and Dr. Franklin C. Behrle (by invitation), Kansas City, Kan.

Clinical observations on over 300 infants reveal that healthy newborn infants pass through four successive stages of respiration characterized by distinct rhythms and patterns (movements of chest and abdomen). The first stage is the period of postnatal adjustment and usually lasts but a few minutes after birth. It is followed by a stage lasting from one to several days after birth, during which the respiratory rhythm is regular and the movements of the chest and abdomen are synchronous. The appearance of retraction of the lower end of the sternum during the first 24 hours of life is an indication that the baby is not well. A mortality rate of 25% has been encountered in such infants, while no mortality has been observed in several hundred infants who had no signs of retraction on the first day of life. The third stage is characterized by variable and changing rhythms and bizarre patterns and lasts several weeks. It is subsequently replaced by a stage in which once more the rhythm becomes regular and the respiratory pattern is more simplified as in the adult.

The effects of varying the oxygen content of respired air on the rhythm, patterns, rate, and per cent change in minute volume have been studied by means of a body plethysmograph and Krogh spirometer. Increasing the oxygen content of respired air to 70 to 90% tends to make irregular rhythms more regular and to convert bizarre patterns into synchronous ones. Lowering oxygen in the respired air to 12% tends to a lesser degree to make regular rhythms irregular, but appears to have no effect in changing the patterns, regardless of whether they are synchronous or bizarre. Increasing the respired oxygen was associated with an increase in minute volume in infants under 3 weeks of age. Lowering the respired oxygen to 12% decreased the minute volume during the first week of life, but increased it in infants over a week of age.

DISCUSSION

Dr. Alfred H. Washburn, Denver: I am interested in asking Dr. Miller a question. Some years ago I did some studies of respiratory rhythms in the first few weeks of life and was interested in how frequently this periodic Cheyne-Stokes type of respiration appeared. I am wondering how many times Dr. Miller saw that appear spontaneously rather than as a response to changes in oxygen.

Dr. Harry H. Gordon, Baltimore: I should like to ask Dr. Miller whether he has any information on the relationship between the behavior of the infant during the first hour of life and subsequent development of seesaw respiration, or retraction.

Dr. Horace L. Hodes, New York: I did not understand from Dr. Miller's discussion whether or not he considered that the decreased minute volume was a result of rapid shallow breathing, in contrast with the more efficient full type of respiration.

Dr. D. O'Brien, Boston: I have been enormously interested in all Dr. Miller has had to say. There is just one question I should like to ask him, which is something that has interested all of us who have been working on this problem at the same time. This extraordinarily unusual feature of a baby who breathes with a lower minimum volume when it is subjected to hypoxia is

something that was also shown by Dr. Cross in his work, and this seems to afford an extraordinarily poor protection to the baby who is, from other causes, subjected to hypoxia. That is, the baby who has something wrong with his lungs from atelectasis and is cyanotic.

I should like to ask Dr. Miller whether he has done any other studies on these babies or other babies which might help us to understand why babies who are subjected to hypoxia, but not artificially, do not in fact just become exhausted with their respirations.

DR. IRVINE MCQUARRIE, Minneapolis: We have recognized for quite a while that an animal or baby can withstand severer degrees of hypoxia immediately after its birth than later and very much better than more mature animals can. Is this related to that phenomenon?

I questioned the claims of refractoriness to anoxia at one time and so put some infant rats, within an hour or two after their birth, into a 100-ml. test tube from which the oxygen had been flushed by nitrogen. I could hardly believe my eyes when I saw these creatures still breathing at the end of 23 minutes with no oxygen whatsoever, just nitrogen, in the respired atmosphere. Call this "anaerobic metabolism," if you wish. Would you comment about that, Dr. Miller, in relationship to your curves?

DR. HERBERT C. MILLER, Kansas City, Kan.: Dr. Washburn, we have not seen periodic breathing in the first 24 hours in babies who were healthy. You do see spontaneous periodic breathing in older infants. You can induce periodic breathing in older infants by subjecting them to low-oxygen atmospheres. You can always produce periodic breathing by subjecting an older infant to low-oxygen atmosphere and then returning him to room air.

Dr. Gordon, we have not been able to find anything in the behavior of the baby in the first hour that will tell us what the subsequent behavior is going to be. Does that answer your question?

Dr. Hodes asked about the rapid shallow breathing. What was the mechanism by which this reduction in minute volume occurred? The reduction in the babies in the first few days of life is brought about by a reduction both in tidal air and in rate. The older infants respond by an increase in the tidal air and a concomitant slowing of the rate. The rates do not become more rapid except in a few of the older infants.

Dr. O'Brien raised the question of the poor defense that this imposes upon the newborn infant. I did not report to you what happens when babies are given 5% carbon dioxide in combination with 12% oxygen or with 20% oxygen. If you subject babies to atmospheres containing a combination of 5% CO_2 and 12% O_2, you get an increase in ventilation amounting to between 100 and 200% of the control period. So that CO_2, even in the presence of rather drastically low oxygen concentrations, produces a tremendous hyperventilation at all ages. You can get the same significant increase in ventilation with combining 5% CO_2 with 20% O_2, and I am beginning to suspect that perhaps the CO_2 is an important part of the defense mechanism. Furthermore, if you give babies oxygen concentrations above the usual room air concentration, 30%, 50%, 80%, and so on, these babies respond uniformly with an increase in their ventilation. There will be, in the first minute or two of this exposure, a decrease in ventilation, but this is then followed by hyperventilation, so that CO_2 and O_2 both seem to be considerable stimulants to the respirations of the newborn infant, and perhaps this answers your question, Dr. McQuarrie.

Blood Levels of Unsaturated Fatty Acids as Indication of Nutritional Requirment for Essential Fatty Acids in Children. DR. ARILD E. HANSEN and DR. HILDA F. WIESE (by invitation), Galveston, Texas.

Blood serum levels for dienoic, trienoic, and tetraenoic acid have been found to correlate with the dietary history, appearance, and histologic characteristics of the skin of dogs maintained on diets containing varying amounts of the essential fatty acids. On the basis of these findings, it appears possible to evaluate the nutritional requirement of infants and children for linoleic and arachnidonic acid by determination of the blood levels of these fatty acids. The semimicro spectrographic method recently developed by the authors was used for determining the serum levels for two, three, and four double-bond fatty acids in four groups of human subjects. The first group was composed of healthy infants and served as the control. The other three groups were composed of 76 hospitalized infants and children, of whom 26 showed good, 21 fair, and 29 poor nutritional status. The average values for dienoic, trienoic, and tetraenoic acids expressed as per cent of the total fatty acids in the fasting serum of the control group were

30.8, 1.9, and 12.5, respectively. The average value for dienoic acid in the well-nourished hospitalized children was slightly lower (28.6) than for the control group, but there was no significant difference for the three and four double-bond acids. The average values for the two and four double-bond fatty acids of the group of 21 hospitalized children in a fair state of nutrition were significantly lower (19.8 and 8.9, respectively) than the control group and the well-nourished hospitalized children. In the malnourished infants and children, these differences were very marked, the average values being 11.6 and 8.0 for two and four double-bond fatty acids, respectively. There was a remarkable similarity in the total amount of the three unsaturated fatty acids in the serum of infants and children in good, fair, and poor nutritional states compared with the results for dogs maintained under strictly controlled dietary conditions and showing good, fair, or poor nutritional states. There was no statistical correlation between the average amount of total serum fatty acids and the nutritional status of the children. These studies indicate, then, that in poorly nourished states human subjects are able to synthesize fatty acids to maintain normal blood levels, but they do not fabricate essential fatty acids in sufficient amount to maintain the levels which are found in healthy infants and children. When linoleic acid comprised about 3.5% of the total calories consumed, children in the control group maintained adequate blood levels for linoleic and arachidonic acid. The minimum requirement for the maintenance of these blood levels has not been determined for human subjects. For the dog the minimum required is about 2% of the calories as linoleic acid.

DISCUSSION

DR. PAUL GYORGY, Philadelphia: I would like to ask Dr. Hansen two short questions. Does he have any comparative data on breast-fed and bottle-fed young infants without any supplementary diet? Second, has he confirmed his original findings on the low essential fatty acid content in eczema in infants, and has he some data on children with other skin diseases?

DR. MILTON RAPOPORT, Philadelphia: I should like to ask Dr. Hansen if he has made any studies at hyperlipemic levels. The child with a nephrotic syndrome with hyperlipemia can present either a state of normal nutrition or of malnutrition, and it would be of interest to know whether there are any differences between levels in hyperlipemia in a child who is in the normal nutritional status and those when he has been in a state of relative starvation for a long period of time.

DR. IRVINE MCQUARRIE, Minneapolis: Whenever I hear Dr. Hansen present a paper on lipid metabolism I am impelled to relate my experience in attempting to substitute for him in an American Academy of Pediatrics round-table discussion on infantile eczema. I expounded the Hansen theory as best I could, pointing out the observed correlation between the reduced iodine, the number of serum fatty acids in afflicted infants, and the occurrence of the skin lesions.

After the meeting a dear old practitioner concerned with therapeutic applications only, came up to me, notebook in hand, and said, "Doctor that was a beautiful message." I blushed with pride for Dr. Hansen until the doctor asked, "Just how much iodine do you give them?"

DR. ARILD E. HANSEN, Galveston, Texas: As regards the question of blood levels in breast-fed babies, we have no information; studies with small infants have not been undertaken as yet, although we hope to be able to do so.

It is the results of our early studies on infants with eczema which led us into the problem of trying to find a chemical method or a method for obtaining exact data concerning specific fatty acids. We have spent considerable time in this effort and finally have reached, we think, the position where we have a tool to assist us in obtaining this factual information. We do not wish to convey the idea that eczema is a simple problem. We do feel, however, at least, that it is being established that unsaturated fats, and particularly linoleic acid, is one of the factors concerned with building healthy skin structure.

If one is interested in reviewing the subject of the essential fatty acids, I may recommend the article by my colleagues Dr. Panos and Dr. Finerty in a recent number of *The Journal of Nutrition*. These workers have reported their results on extensive histologic studies of various tissues of the body.

As regards the hyperlipemia phenomenon, that is exactly the reason why we have chosen to express our values as per cent of the total faty acids. One obtains a grossly different idea by

expressing them in absolute values such as milligrams per 100 cc. On the other hand, one could use the absorption coefficient $E^{1\%}_{1\,cm.}$, which expression I am afraid might scare some of us from even considering the problem in detail. We do know this: from a few instances in which we have taken lipemic serum, the unsaturated-fatty-acid percentages are lower than those in this series. We hope to obtain further information on the subject of lipemia.

The Minimal Requirement of Infants for Certain Amino Acids. Dr. Selma E. Snyderman (by invitation), Dr. Edward L. Pratt, Dr. Mung W. Cheung (by invitation), Dr. Emmett Holt Jr., New York, Dr. Theodore C. Panos (by invitation), and Dr. Arild E. Hansen, Galveston, Texas.

A knowledge of minimal amino acid requirements for infants and children is of self-evident importance, especially in the planning of diets for populations in areas where good protein is scarce and in constructing an ideal parenteral nutriment. Of even greater usefulness would be the discovery of a definite biochemical measurement or a clear-cut clinical sign whereby one could reliably diagnose a deficiency of a specific amino acid.

The determination of minimal requirements of particular amino acids involves practical difficulties. It is necessary to vary the intake of the amino acid being studied, maintaining a diet which is otherwise adequate in all respects. Two techniques have been employed in the past: (1) a diet using mixtures of pure amino acids, composed in part of *d-l* forms, and (2) one in which degradation procedures are applied to natural proteins or hydrolysates to destroy particular amino acids, which are then replaced at desired levels. Both of these procedures are open to criticism. The use of unnatural isomers involves giving substances whose effect is unknown; some *d* forms are known to be toxic for animals. The degradation procedures, on the other hand, do not exclude the possibility that substances of unknown nature and function are produced. At long last it has become possible to avoid both of these difficulties, for it is now possible to obtain all the amino acids—both essential and unessential—in quantities suitable for conducting studies in infants.

We have undertaken to ascertain the amino acid requirements of the growing infant by the use of diets in which the protein moiety was supplied by mixtures of *l* amino acids, both essential and unessential. Our basal diet was based on the amino acid composition of breast milk. By means of withdrawal and stepwise supplementation of particular amino acids, an attempt has been made to ascertain the minimal amount of amino acid which would be consistent with normal weight gain, normal nitrogen retention, and maintenance of plasma protein. Preliminary observations are presented in regard to two amino acids—threonine and phenylalanine. The minimal requirement for threonine appears to be between 45 and 70 mg. per kilogram of body weight (between one-half and three-fourths of the quantity provided by breast milk). The minimal requirement for phenylalanine appears to lie between 61 and 91 mg. per kilogram (between two-thirds and three-fourths of the quantity provided by breast milk).

Study of the excretion of free amino acids in the urine in these patients by means of paper and column chromatography showed that there was a decrease in the amount of free threonine excreted in the urine when threonine intake was below the minimal requirement for that infant, without significant change in the total amount of free amino acids in the urine. A similar correlation was found for free phenylalanine in the urine and intakes of phenylalanine below the minimal requirement.

Reddening of the oral mucous membranes was promptly associated with deficiency of threonine. No clinically observable alterations resulted from a few days of phenylalanine-deficient intake.

DISCUSSION

Dr. Irvine McQuarrie, Minneapolis: I would like to ask a question that has been bothering me. Have you studied the effect of hormones, for example, adrenal or pituitary somatotropic hormones, thyroxin, or testosterone, on the problem involved here?

Dr. Frank H. Tyler, Salt Lake City: Dr. Armstrong in our laboratory has been interested in the metabolism of phenylalanine.

In the course of these studies, we have administered synthetic amino acid mixtures deficient in phenylalanine to patients with phenylpyruvic oligophrenia. On this regimen the phenylketonuria disappears and the serum phenylalanine falls to normal when the phenylalanine is adequately restricted.

On reintroducing phenylalanine to the diet at this time, we find that considerably less than the amounts reported here as the normal requirement can be tolerated without biochemical relapse occurring.

I think the explanation is not difficult. There almost certainly is an obligatory degradation of phenylalanine to tyrosine in normal persons which increases the requirement for phenylalanine beyond that actually needed for growth and utilization as such. In these children this pathway is completely blocked, and therefore they require very much less phenylalanine than the normal children.

DR. DANIEL C. DARROW, New Haven, Conn.: Am I right that all the reduction in proteins was in the globulin fraction? If this is so, it is surprising, since undernutrition usually leads to greater loss of globulin than albumin.

DR. HARRY A. WAISMAN, Madison, Wis.: These workers are to be congratulated because all these feeding and balance studies are very difficult. Despite the fact that they used three patients, it is an enormous amount of work.

There are several things I would like to inquire about. If I understood correctly, there was rather little loss of other amino acids in the urine during the period when the specific amino acid was deficient. This is a little unusual, if not surprising, because when all the amino acids are present except one, they are all lost, or presumably lost, and we can take some experience from animal studies in that respect.

Dr. Pratt didn't say anything about it, but I assume, because the infants lost weight, that their food intake was decreased. I should just like to know if that was true.

There is one interesting aspect which Dr. Tyler brought out which I think merits a little emphasis, and that is I think it would be very interesting if, in subsequent work, these workers would feed higher amounts of either glycine or glutamic acid, since these so-called nonessential amino acids function to supply a source of amino groups which can be transaminated into structural amino acids which form the framework of the protein molecule. I think that by increasing the levels of the nonessential amino acids, one might get by with smaller amounts of the essential amino acids.

DR. IRVINE MCQUARRIE, Minneapolis: Can one amino acid spare another, and have you doubled up on leaving out two at a time, because that can greatly accentuate the disturbance?

DR. EDWARD L. PRATT, New York: We opened this paper with a statement of the need for data of this kind. The only paradox in this situation is one of words and deeds. There are many words but very few deeds in the form of support for such research.

Dr. McQuarrie should stop asking these questions, because if you were to study these patients with all the possible variations in their diet, it would really drain Fort Knox.

We have not attempted to experiment with hormones, although we don't have any doubt that depending on whether you are growing rapidly or slowly, your requirements are different. If you are building up a specific kind of tissue, your requirements are different, because very likely the amino acid requirement for the whole baby is merely the summation of the special requirements for each individual tissue. And when you are building a certain tissue, you need more of certain amino acids than when you are building a different one.

Now, whether one amino acid can spare another is a little bit of a problem in semantics, that is, the meaning of "spare." However, if you have a diet which is minimal in all the essential amino acids, and then you leave one of them at the minimal level and raise all the rest to double, then the patient or the animal gets into trouble, when he was in no trouble on the minimal requirement. This is because the new diet changes the need for this one left at the very low level.

We have been interested in Dr. Tyler's work with this type of patient (phenylpyruvic oligophrenia). We have searched diligently for such a patient to study; but I think really the importance of their observations is that it opens up a whole new field of possible investigation for the study of abnormal metabolism, and, particularly, it looks as though there might even be possibilities for therapeutic measures.

The serum protein determinations, done in the crude way that we did them, showed that most of the change was in the globulins, but I think that is consistent with the composition of the proteins. Both phenylalanine and threonine are present in larger amounts in the globulins, and their turnover rate probably is faster than for albumin; it seems all right to me.

I am not quite sure I understood Dr. Waisman, but I think he felt we should have found in the urine a lot of alpha-amino nitrogen when the patients were fed no threonine or phenylalanine. That was not the case. The actual total of the amino acids measured in the urine differed less than 5% in either case.

What you do find is that immediately on dropping an essential amino acid, there is a large outpouring of urinary nitrogen, but this is not alpha-amino nitrogen, nor do we find that for these two amino acids the rest of them come out in abnormal quantities.

I think that there has been some thought that this happens, and it may occur with some other amino acids. But I feel fairly secure, at the moment, subject to revision, that it doesn't happen with these two.

The Minimal Nitrogen Requirement of Infants and the Effect of Vitamin B_{12} upon It.

Dr. Robert Kaye, Dr. Ronald H. Caughey, and Dr. Wallace W. McCrory, Philadelphia.

Episodes of restricted food intake occur frequently in infants. Determination of the minimal requirement for nitrogen equilibrium in this age group should provide information of value in minimizing or obviating the occurrence of severe nitrogen deficits following such episodes. Our interest in this problem grew out of studies designed to evaluate the effects of vitamin B_{12} on nitrogen retention. The clinical studies of Wetzel and Chow have shown that a large percentage of children who are malnourished or suffering from a variety of clinical illnesses show improved growth progress following the oral administration of vitamin B_{12}. The question which we sought to answer was, "Is the growth-promoting effect of vitamin B_{12} a manifestation of a specific positive effect on nitrogen retention, or is its activity a reflection of some other mechanism, such as increased appetite, with consequent increase in caloric intake?"

In order to explore this question more fully, our subjects were divided into two groups and were fed with constant levels of nitrogen and caloric intake. One group of three subjects was given a high-nitrogen intake of approximately 1 gm. per kilogram of body weight per day, and another group of three comparable subjects was given a low-nitrogen intake of approximately 100 mg. of nitrogen per kilogram per day.

The data which we wish to present today fall into two categories: one, the definition of the minimal nitrogen requirement for equilibrium under the conditions of our experiment of infants between the ages of 4 and 12 months and two, the effect of vitamin B_{12} on nitrogen metabolism in infants.

The data relating to the determination of the minimal nitrogen requirement for equilibrium are derived from balance studies performed on five boy babies whose nitrogen intake approximated 100 mg. per kilogram and whose caloric intake averaged 107 calories per kilogram per day. The diet consisted solely of a cow's-milk modification generously supplemented with vitamins A, B, and C, thiamine, riboflavin, nicotonic acid, pyridoxine, and pantothenic acid. The formulas were prepared from a powdered milk of low-protein content to which were added olive oil and glucose to bring the caloric value up to the desired level. The percentage of the calories derived from protein was 2.2, carbohydrate — 50.4, and fat 47.3. Balances were carried out for nitrogen and the electrolytes sodium, chloride, and potassium after a four-day period of adjustment on the low-protein diet. It was found that three to six days were necessary in order to achieve fairly stable minimal levels of urinary nitrogen excretion on transition from a normal- to a low-protein diet. The duration of the balance periods averaged 11.6 days and ranged from 10 to 12 days. The intake averaged 98 mg. N_2 per kilogram per day (range, 70 to 110). The nitrogen retention averaged — 2 mg. per kilogram per day (range — 20 to $\pm$ 20). The average weight gain was 1 gm. per kilogram per day. Both patients given more than 100 mg. per kilogram per N_2 day were in positive balance.

In contrast, three similar subjects receiving an average nitrogen intake of 870 mg. per kilogram per day showed an average nitrogen retention of 269 mg. per kilogram per day and a weight gain of 13 gm. per kilogram per day.

I would like to consider the results of our studies on the effects of vitamin B_{12} on nitrogen retention in infants maintained on constant dietaries at high and low levels of nitrogen intake. The duration of the balance periods was 4 to 6 days for the high-protein- and 10 to 12 days for the low-protein-fed subjects. The dosage of vitamin B_{12} was 30 to 300 γ per days by mouth.

In the high-protein-fed subjects, vitamin B_{12} failed to produce an increase in nitrogen retention. There was a decrease in nitrogen retention with B_{12} administration from 269 to 213 mg. N_2 per kilogram per day. As this difference represents only 5% of the intake, it is not considered a significant decrease.

The control- and treatment-period nitrogen retentions in the low-protein group were 3 and 20 mg. per kilogram per day. Although this change is equivalent to 17% of the nitrogen intake, it is of questionable significance in view of the fact that a large percentage of the observed difference is encountered in a single subject.

Changes in rate of weight gain in both groups of subjects were in the same direction as the changes in nitrogen balance. For the high-protein group the values for control and treatment periods were 13 and 11.5 gm. per kilogram per day and for the low protein group, 2.0 and 2.9 gm. per kilogram per day.

Vitamin B_{12} administration was associated with a 25% increase in urinary nitrogen excretion, a change which might be a reflection of an enhanced conversion of amino acids into fat or carbohydrate as suggested by animal experiments of others.

DISCUSSION

DR. NATHAN B. TALBOT, Boston: A normal person receiving a constant caloric intake requires approximately 18 days to regain nitrogen balance following a sudden change in protein intake. If the present studies were carried out within this period of time, one wonders whether the changes described might not have been reflecting this adaptation to low-protein intake rather than effects of vitamin B_{12}.

DR. L. EMMETT HOLT JR., New York: I would like to ask Dr. Kaye if he ever used a postcontrol period. Did he follow up the B_{12} period by a period without B_{12}?

DR. ROBERT KAYE, Philadelphia: In answer to Dr. Talbot's question, our subjects were able to achieve minimal levels of urinary nitrogen excretion in four to six days following transition from a normal to a low-protein diet. It is fairly likely that following further periods of adjustment they might have been able to achieve equilibrium at lower levels of nitrogen intake than those used in our subjects. In regard to the question of whether or not vitamin B_{12} was administered for a sufficiently long time to detect an effect on nitrogen retention, three subjects have been studied for balance periods of 24 and one subject for 20 days without unequivocal effects.

In answer to Dr. Holts's question, we did not employ postperiods without B_{12} administration. They would have been interesting, but would have added to the cost of the study.

DR. IRVINE MCQUARRIE, Minneapolis: I would like to ask if any of these infants had anemia of any kind.

Some Effects of Thyroid or Thyroxin upon Premature Infants. DR. STUART S. STEVENSON and DR. T. S. RANOWSKI (by invitation), Pittsburgh.

Forty-eight premature infants, whose condition seemed satisfactory at one week of age and whose weights approximated 1,500 gm. were selected for this study. Even-numbered infants in the series were given daily doses of desiccated thyroid or thyroxin for periods averaging three and one-half weeks; odd-numbered infants were given placebos of lactose according to the same schedule. The clinical progress of the infants was noted and weekly red blood cell counts and hemoglobin and serum protein-bound iodine levels were determined.

Daily doses of 1 or 2 grains (0.065 or 0.130 gm.) of thyroid produced no significant effects upon clinical condition and progress or upon the serum protein-bound iodine level. Daily doses of 3 grains (0.194 gm.) of thyroid or 0.2 mg. of thyroxin did not affect the caloric and fluid intake, the gavage incidence, the amount of vomiting, the skin color, or the body temperature. Such dosage, however, decreased the weight gain, increased the pulse rate, and increased the incidence of diarrhea. A higher percentage of infants so treated required blood transfusions

and did not fare so well clinically. The level of serum protein-bound iodine was elevated. The administration of thyroid or thyroxin to premature infants selected as noted above is therefore without observable benefit and is sometimes harmful. The effects of daily dosage with 0.2 mg. of thyroxin were at least as great as those with 3 grains of thyroid.

The mean serum protein-bound iodine level of 32 untreated infants was 5.7 ± 0.47 at an average age of 9 days, and mean values for the control infants did not differ significantly from this figure during a subsequent five-week period. These levels do not suggest that the premature infant is deficient in circulating thyroxin.

Thyroid doses exceeding 2 grains per day are necessary to produce pharmacologic effects in premature infants and in euthyroid children and adults. This implies that the thyroid gland of the premature infant produces and releases thyroxin in amounts comparable to those of normal older human beings and approximating 2 grains of thyroid per 24 hours. Medication of the athyrotic cretin should be adjusted with this in mind.

Hunger or failure to gain weight usually determined the caloric intake of the infants in this study. On such a self-regulatory regimen, they ingested an average of approximately 150 calories per kilogram of body weight per 24 hours, and their average weight gain exceeded 30 gm. per day. This large weight increment may be explained in part by the fact that they were in good health, more than one week of age, and over 1,500 gm. in weight when they were selected for observation. The high caloric intake, however, must have been important and does not seem to have been harmful.

DISCUSSION

Dr. Bela Schick, New York: At the last International Pediatric Congress in Zurich, Moncrief talked again about giving thyroid to premature children. He told us that the nurses particularly were satisfied with the effect of this thyroid treatment in premature children.

I thought it worth while to take it up at our service, and Dr. Donowitz studied about 30 premature babies, with controls, some of them twins.

We gave them thyroid in the first week of life. We didn't see much difference in giving it later or earlier. I was very much dissatisfied. We gave only ¼ or ½ grain (0.016 or 0.033 gm.) a day for two or three weeks. We were not only dissatisfied with the lack of effect, but we saw even with these small doses the symptoms which Dr. Stevenson mentioned. Some of the children showed diarrhea and vomiting. So we discontinued the study. I agree entirely that we should stop this treatment.

Dr. Harry H. Gordon, Baltimore: I should like to ask Dr. Stevenson whether he has any observations on excretion of creatine in the urine of the infants given thyroid.

It is of interest that the weight gains in these two groups of infants were the same and that the caloric intakes were the same. This implies that the metabolic rates must have been the same. We once studied an infant given thyroxin who responded clinically as outlined by Dr. Stevenson with irritability and diarrhea, but for whom we could demonstrate no rise in basal metabolism.

I really would like to address most of my comments, though, to the question of the total caloric intakes of these infants. Dr. Stevenson said that his results were essentially in agreement with the studies of Horton and of Hardy, and I happen to have direct contact with both these studies. The studies of Horton and Lubchenco were in Denver. The caloric intakes of these infants fed on a self-regulatory method— that is, the amount of food given was based on the nurses' interpretation of hunger—varied from 85 to 150 calories and averaged only 120 for the group.

From Baltimore, Dr. Hardy and Dr. Goldstein have reported that if premature babies are fed on self-regulatory schedules, they ingest much larger amounts, and I spend part of my time now trying to convince some of the people in Baltimore that their babies too will gain satisfactorily on the smaller intakes.

Last night, Dr. Albert Dorfman had occasion to tell some of us rather pointedly that the bias of the principal investigator sometimes leads to an unconscious interpretation of certain symptoms and signs by his associates, and I think that this may explain part of the difference between Baltimore and Denver.

Dr. Stevenson said that his babies were fed at pleasure. For the 25% of the babies reported as being gavaged, at whose pleasure? And even for the babies that weren't being gavaged—

we have to rely on an interpretation of hunger by the nurses. We have always subscribed to the statement in the last available edition of the Holt and McIntosh textbook that premature babies should be fed the minimum amount of food on which they gain satisfactorily, and then one adds to that, "and which keeps them happy."

I suppose this represents the bias by which infants in Denver seem to be satisfied with less food than the infants in Baltimore. In one hospital with which I am connected, it was interesting to find that all the little babies seemed to require high caloric intakes to satisfy them. When we traced this, we found out that there was one nurse on the evening shift responsible for the report that all the babies were hungry.

Dr. Lawson Wilkins, Baltimore: I was interested in this paper from two standpoints. In the first place, a few years ago, it was claimed that androgen in the form of methyl testosterone might stimulate the growth of the premature baby. An experiment was made by Dr. Janet Hardy and myself in Baltimore. Premature infants of different birth weights together with paired controls were given methyltestosterone and fed a liberal diet with constant calories per kilogram. We showed that this hormone had absolutely no effect in accelerating the growth or weight gain of the premature infants. In contrast to this, children of older ages and adults do show an excellent protein-anabolic effect from androgen. I think this is because the premature infant is already one of the most protein-anabolic animals that exists, and doesn't need any help from pediatricians if he is given adequate dietary intake.

An interesting point to me was the use of this method in attempting to determine the physiologic output of the thyroid gland in prematurity. We certainly would agree with the idea that up to the level of physiologic output one never gets effects of thyroid. Thyroid is a perfectly worthless substance to the human being given up to the physiological level, provided he has a normal thyroid gland. When it is administered in full physiologic dosage, the gland is simply put to rest. From experience with athyrotic cretins, I feel that a completely athyrotic child during the first year or two of life can be brought to a state of euthyroidism by a daily dose of ¾ or 1 grain (0.049 or 0.065 gm.) of thyroid instead of 2 grains (0.130 gm.). Does this mean that the premature infant is normally at a higher level of thyroid activity?

Dr. Irvine McQuarrie, Minneapolis: This impresses me as being something really added to our previous knowledge and our former practice. I am happy when people are not trying to speed up the premature infant any more, not trying any kind of medication on him, and just let him go, as has been remarked. Give him the proper environment and the essentials, and let him go at that.

Dr. Charles Hendee Smith, New Brunswick, N. J.: I am not a "calorimeter," but I have had a long experience with premature infants. I agree heartily with Dr. Gordon that the best amount is the smallest amount on which any baby does well. I will go one step further than he does and say that a great many premature babies do very well, amazingly well, on 100 calories per kilogram, not even as high as 110.

Moreover, the self-demand feeding schedule which is so stylish today never works. People always get into a mess in private practice with it, and they are glad to be put on a schedule. The self-demand feeding always means that the mother or nurse stuffs more food into the baby than he really needs. I believe in "scientific underfeeding."

To try to give 150 calories per pound (453.59 gm.) "on demand" to any baby is not necessary and may be dangerous.

Dr. Stuart S. Stevenson, Pittsburgh: I should like to thank Dr. Schick for his remarks. I should like to say to Dr. Wilkins that our thoughts on the output of the thyroid gland were a sort of by-product of the study, and we allowed ourselves a little speculation about this.

Dr. Smith has quoted his own saying, and that of many others, that the smallest amount you can feed a premature baby, and have him gain and do well, is the best amount. This is a fine thought, but it costs between $500 and $1,000 to rear a premature baby in the hospital, depending on how little he is. If one can halve the time of the hospital stay, I think it is distinctly worth while.

We did not study cretins, to answer Dr. Gordon. The 120 calories per kilogram—was that for premature babies of all weights? All 48 babies in the present series weighed more than 1,500 gm. at birth. Although 25% of the 48 were gavaged, one or more times, only 4 infants, or 8% of the total, were gavaged for appreciable periods.

As far as the high intake goes, it was most embarrassing to Dr. McCluskey and me, who have constantly preached what Dr. Smith has just brought up. "Give them as little as they can get by on, happily." I was horrified when we went over the work sheets and found the babies averaging 150 calories per kilogram, thanks to the kindness of the residents and nurses. I think they hadn't read Dr. Gordon's papers! But I went back and read them. Dr. Gordon, if you will remember, calculated the basal metabolic needs and then finally added a certain amount for growth, which I believe was based on an increment of 12 gm. per kilogram per day. If you take Dr. Gordon's same formula and plan to have the baby gain 30 gm. a day, which resembles the amount he would be gaining in utero, you come out with the baby needing about 150 calories per kilogram.

Blood Galactose in Infants and Children. Dr. Alexis F. Hartmann, St. Louis.

In a number of near-normal and sick infants under a variety of circumstances in regard to feedings, determinations were made of the total "true" blood sugar by the Somogyi method of protein precipitation with zinc both before and after fermentation by yeast. In this way glucose and galactose were separated. From such studies the following conclusions were reached:

1. Under ordinary conditions of milk feedings in near-normal infants, as much as 40% of the blood sugar may be galactose.

2. When unusually large amounts of galactose are fed to such infants, e. g., 1.75 gm. per kilogram of body weight, a blood sugar curve very similar to that seen in a normal glucose tolerance test results, with the exception that the rise of sugar is due entirely to galactose. During the early rise of the galactose value, the glucose value may fall and then rise later as the galactose value falls.

3. In essentially normal infants receiving no lactose- or galactose-containing food, zero values for galactose and normal values for glucose may be expected.

4. In infants with galactosemia, receiving lactose or galactose feedings, high values of blood galactose are to be expected, and if galactose and glucose values are not separately determined, hypoglycemia may escape detection. The presence of small amounts of galactose in the blood of such infants when not receiving lactose- or galactose-containing food suggests formation of galactose from glucose.

5. In infants with diarrhea, when fed milk after a period of starvation or nonmilk feeding, hypoglycemia may also escape detection unless glucose and galactose values are individually determined. The frequent high blood galactose values seen in such infants, even while underfed, suggest temporary partial "galactosemia," perhaps the result of illness and milk deprivation.

DISCUSSION

Dr. George M. Guest, Cincinnati: I should like to ask, Dr. Hartmann, if you have determined levels of blood galactose in diabetic patients during apparent insulin reactions which sometimes occur when the blood sugar, determined by usual methods, is within normal range; also, if you have performed fructose tolerance tests on patients with abnormal galactose tolerance curves.

Dr. Robert L. Jackson, Iowa City: Seven children with galactosemia have been observed in our clinic. We have found that the galactosemia persists for a period of months after the patient is receiving a galactose-free diet. During this period the liver gradually decreases in size. Apparently, a relatively long period is necessary to deplete the storage of galactose in the liver. All patients have had a recurrence of galactosemia and galactosuria after receiving a diet containing lactose. Our observations suggest that this inborn error of metabolism is permanent.

Dr. Daniel C. Darrow, New Haven, Conn.: I should like to ask Dr. Hartmann really only one question. Does he believe that the defect in the transient galactosemias involves chiefly the enzymes of the intestinal tract or the liver? I would surmise that both are involved. Why should the enzyme seem to decrease temporarily in these infants?

Dr. Irvine McQuarrie, Minneapolis: The one compound in the body that I know of that contains galactose is cerebroside in the brain. I should like to ask Dr. Hartmann if he

knows of any studies that have been made with regard to its content in these patients. Could this congenital anomaly of the metabolism have anything to do with the mental retardation, which is a very real thing in these afflicted babies?

DR. ALEXIS F. HARTMANN, St. Louis: Dr. Guest's question is a most natural one, and we did look into the matter of reactions in diabetic children, which seemed perhaps not to be related to a properly low blood sugar value. As yet, Dr. Guest, we have not been able to demonstrate any markedly increased galactose value in such children, although the usual values after a meal that contains a good big glass of milk will be found to be as much, perhaps, as 15 mg. per 100 cc. during the first hour or two after the meal.

We began our investigations with as simple a setup as possible, and we chose only those infants who were getting either lactose, as the carbohydrate, or dextri-maltose, which would give only glucose, and we purposely avoided fructose so as not to complicate matters, because we weren't quite ready to run fructose along with galactose and glucose. That certainly should be the next step, and as one follows such infants, one ought to be able to say how much fructose, how much glucose, and how much galactose are in the blood at any one time.

I did not intend to call your attention especially to the previously described type of galactosemia. I merely wanted to bring out the possible significance of glucose and galactose in different types of hypoglycemia. I would like to add, however, that in otherwise normal animals many of the symptoms of galactosemia, including cataracts, result from the continued feeding of either lactose or galactose in large amounts; whereas other carbohydrate substances fed to those animals are without such toxic symptoms. So apparently just the continued accumulation of galactose is what is troubling the animal and the human.

Now, Dr. Darrow asked about the cause of transient galactosemia. I haven't gone further in my own mind than to liken it to disuse diabetes. If one does not give glucose or other carbohydrate to human beings for any length of time, a transient diabetes results, which seems to be on the basis of a sort of disuse atrophy of the beta cells. One would think that either galactokinase drops to a low level and takes a few days to come up again, or that galactowaldenase or its coenzyme does.

This is where I would like to proceed next; I would like to see whether the coenzyme simply doesn't pass out of the picture, because it apparently is not needed for anything else except this one specific transformation of galactose-1-phosphate to glucose-1-phosphate.

The coenzyme might be a nice tool. One could perform galactose tolerance tests with and without the feeding of the coenzyme and see whether one reverses the process of transient galactosemia.

I know nothing about studies of the brain cerebrosides, especially those which when hydrolyzed yield galactose. It might be a good thing to look into to explain the cause of some types of mental deficiency.

Neutral 17-Ketosteroids of Plasma in Children. DR. LYTT I. GARDNER, Syracuse, N. Y.

A technique has been devised which measures, it is believed for the first time, the endogenously produced 17-ketosteroids of peripheral human plasma. Contrary to previous thought, the 17-ketosteroids of plasma appear to be tightly bound to plasma proteins. Ether extracts were made of acid-hydrolyzed plasma and were partitioned between hexane and ethanol. The steroids were chromatographed on magnesia, silica-gel columns and the concentration estimated by a micro-Zimmermann procedure. Plasma neutral 17-ketosteroid concentration in 15 normal men was 74 ± 7 γ (mean $\pm$ standard error of the mean) per 100 cc. and in 10 normal women 60 ± 8 γ per 100 cc. The error in replicate determinations of a sample was 6.8%. Prepubertal children showed plasma concentrations of < 3 γ per 100 cc., as did an oophorectomized-adrenalectomized woman. Normal full-term infants showed a range of plasma concentrations between 70 and 150 γ per 100 cc. in the first 48 hours of life, with progressive fall to unmeasurable values by the end of the first week of life. Three children between the ages of 7 and 13 years with untreated congenital adrenal hyperplasia showed plasma concentrations from 80 γ per 100 cc. to 360 γ per 100 cc. Plasma concentrations fell to less than 16 γ per 100 cc. on treatment

with cortisone. A woman with virilizing adrenocortical tumor showed a plasma concentration of 310 γ per 100 cc. Premature infants exhibited very high values, the maximum being 533 γ per 100 cc. in a 2 lb. 8 oz. (1,135 gm.) baby on the second day of life. Unlike those in full-term infants, plasma 17-ketosteroid concentrations remained elevated in premature infants for as long as 40 days.

The above can be summarized as follows: 1. Endogenously produced 17-ketosteroids of peripheral plasma appear to be protein-bound. 2. Plasma 17-ketosteroids are increased during the first week of life, after which very low values prevail until adolescence. 3. Children with congenital adrenal hyperplasia have plasma 17-ketosteroid concentrations in the adult range or higher. On therapy with cortisone these values fall to normal for their age. 4. Premature infants have plasma 17-ketosteroid concentrations greater than full-term newborn infants, and these values are abnormally persistent.

DISCUSSION

Dr. Alfred M. Bongiovanni, Baltimore: Dr. Gardner's paper certainly should help us to a great extent to evaluate the role of renal function in the excretion of steroids. About three years ago, we were very much concerned by the extreme variation in the excretion of 17-ketosteroids under unusual circumstances, such as with the marked oliguria of nephrosis, which in time might be accompanied by a burst of diuresis.

On the first day of diuresis, these appeared to be abnormally high. It would seem that Dr. Gardner's contribution should help to clarify some of the set things by relating blood levels to urinary excretion.

Dr. Stewart H. Clifford, Boston: I have been asked by Dr. Clement Smith, who couldn't be here today, to ask a question as to what, if any, practical implication this has to the treatment of the newborn premature infant. We are anticipating questions that may be raised in view of this and Dr. Klein's paper.

Dr. Sobel, Cincinnati: Dr. Gardner's contribution is a welcome and impresssive one. I wonder whether the sensitivity of the method, which evidently limits its usefulness in pre-adolescent children, might be increased by measuring the total ketonic steroid content of the plasma as well as the neutral 17-ketosteroids. A technique being developed by Dr. Leland C. Clark, in Yellow Springs, allows us to measure the total neutral ketonic steroid content of urine and to fractionate it colorimetrically by varying the conditions of the test so that 3-, 17-, and 20-ketosteroids can be individually estimated.

The procedure has been applied to the neutral lipid extract of acid-hydrolyzed urine collected from a 12-year-old boy who has congenital adrenal hyperplasia. The 17-ketosteroid excretion (Zimmereman) was about 130 mg. per day and represented only approximately 45% of the ketonic material, of which about 300 mg. was excreted daily. The 3- and 20-ketosteroids composed about 25% of the total. We can probably regard these steroids as biologically significant, since the excretion of all the components, including the total as well as the Zimmerman reactive material, was markedly reduced, to about 20% of the control values, when the patient was treated with cortisone.

Normal children also excrete substantially more total ketonic steroids, as measured by this procedure, than they do Zimmerman reactive steroids.

Should a similar relationship exist in the plasma, it might prove feasible to determine the total ketonic steroid content of a plasma sample, even when the 17-ketosteroid concentration is too low for satisfactory estimation.

Dr. Robert Klein, Pittsburgh: I would like to add my word of admiration for this very important piece of work of Dr. Gardner's. Dr. Gardner was kind enough to examine some specimens on some of our patients with adrenal hyperplasia, and on one patient we had a sample before and two hours after administration of corticotropin (ACTH). Unfortunately, I think, as we will find from Dr. Kelley's paper, this patient was a sport in that her circulating Compound F-like substance was in the normal range to start with and went from 9 to 20 γ per 100 cc. after the administration of corticotropin.

However, her ketosteroids reported by Dr. Gardner started at the high level of 100 and advanced only to 120 γ per 100 cc.

DR. HENRY L. BARNETT, New York: Although as usual one is unable to say whether for good or bad, it is apparent that the renal clearance of 17-ketosteroids in the premature infant is considerably below that of the adult, since at a higher concentration in plasma the rate of excretion is lower.

DR. CHARLES A. JANEWAY, Boston: I would like to congratulate Dr. Gardner, and, as a specialist in kidney diseases, ask him if he has any data on patients with real renal insufficiency.

DR. LYTT I. GARDNER, Syracuse, N. Y.: I would like to thank the discussers for their kind comments. I notice nobody asked me how accurate the method was.

As for Dr. Clifford's comment, I believe that we are still at too early a stage in our knowledge to make any statement concerning the implications of this insofar as therapy might be concerned in premature infants or the normal newborn infants. This is an extremely rapidly moving field, as we can all see, and I think most of us need some time to sit down and think about what are the implications of low plasma Compound F, high plasma 17-ketosteroids, disappearance of the adrenal reticular zone, proliferation of the cells of the adrenal zona fasciculata, and so forth, all of which make a complicated and dynamic picture. I am afraid I will have to renege on that answer at the moment.

As for Dr. Sobel's comment, of course when one is working in the field of methology, one is always apprehensive of not making an adequate recovery, or of overestimating, which is why we applied for color-correction calculations of Willard Allen. I think it would be valuable to apply another type of color reaction quite different from the Zimmerman reaction as a check, or as a way of telling us that steroids other than the 17-ketosteroid group might better elucidate some of these problems.

I want to thank Dr. Bongiovanni and Dr. Klein for their comments.

Dr. Barnett mentioned the knotty problem of what do these data mean with respect to renal function; if one does clearance arithmetic on what data we have already, it becomes quite apparent that the clearance numbers are extremely low in the premature infant. Insofar as milliliters per 1.73 square meters of surface area per minute in the normal adult, they range between 9 and 21.

It is of some interest to us in terms of milliliters per 1.73 square meters per minute that the values were very close to glomerular filtration rate. Those were patients who had extreme endogenous overproduction of 17-ketosteroids. In a sense, they had an endogenous load of 17-ketosteroids.

We wonder then if this does not imply that the 17-ketosteroids act as threshold substances to the kidney. There is one experiment to support this, some work of West and colleagues, who infused testosterone into patients and measured the free testosterone in the plasma. They found, upon testosterone load, that renal clearance went right up to glomerular filtration rate but did not exceed it.

As for Dr. Janeway's comment, we have not yet had an opportunity to study renal insufficiency, unless one would take the experiment on myself with probenecid (Benemid), which I do think is a form of temporary renal insufficiency. I think that would be very worth while as a project.

Circulating Adrenal Hormones in Children with Endocrine and Other Disorders. DR. VINCENT C. KELLEY and DR. ROBERT S. ELY, Salt Lake City.

Techniques for the more precise and definitive evaluation of the functional status of the pituitary-adrenal system have been developed and subjected to some preliminary clinical evaluation during recent years. During the past two years, in human and animal studies, we have applied several of these techniques, including the determination of (1) plasma 17-hydroxycorticosteroids by the method of Nelson and Samuels which employs the phenylhydrazine color reaction chromatographed plasma; (2) urinary 17-hydroxycorticosteroids by the technique of Glenn and Nelson, a modification of the above technique using preliminary beta-glucuronidase hydrolysis of urine; (3) circulating levels of endogenous corticotropin (ACTH) by the technique of Sydnor and Sayers, a modification of the adrenal ascorbic-acid-depletion technique employing preliminary concentration by the Astwood oxycellulose technique, and (4) the fluorometric technique of Sweat and Farrell for plasma corticosterone and 17-hydroxycorticosterone.

Although most of the data to be presented have been obtained by the first of these techniques, certain correlative data obtained by the other methods will be included.

Data concerning the responses of plasma 17-hydroxycorticosteroids to stimulating agents such as cortisone, epinephrine, and corticotropin in different forms and dosage schedules will be presented. These data reveal the following: (1) variation in response to corticotropin, depending upon the dosage form used, (2) more prolonged elevation of 17-hydroxycorticosteroids in response to intramuscular cortisone than to the other hormones studied, (3) complete lack of correlation between eosinophile and 17-hydroxycosteroid responses to epinephrine, and (4) no necessary correlation between the responses of eosinophiles and of 17-hydroxycorticosteroids to corticotropin. It appears that the response of 17-hydroxycorticosteroids to corticotropin injection constitutes a more reliable criterion of adrenal cortex function than does the eosinophile response test.

Plasma 17-hydroxycorticosteroid concentrations and their responses to injection of stimulating agents have been determined in normal children and in children with a variety of metabolic and endocrine disorders and various acute and chronic illnesses, including relatively large groups of patients with congenital adrenal hyperplasia, treated and untreated epilepsy, and rheumatic fever in various stages of therapy with different therapeutic regimens. In some of these children plasma concentrations of corticosterone together with a comparison of 17-hydroxycorticosteroid values obtained, from identical plasma samples, by the fluorometric method of Sweat and by the method of Nelson and Samuels will be presented.

Circulating corticotropin levels were obtained in normal children, in children with congenital adrenal hyperplasia and rheumatic fever before, during, and after hormone therapy, and in children with miscellaneous disorders. Elevated levels were observed in patients with congenital adrenal hyperplasia, acute rheumatic fever, Sydenham's chorea, and spontaneous hypoglycemosis. These data will be presented and correlated with data concerning 17-hydroxycorticosteroids in the same individuals.

Animal and human experiments concerned with the influence of salicylates, ascorbic acid, and certain enzymes and metabolic products on plasma and urinary 17-hydroxycorticosteroids have been performed and will be briefly mentioned.

DISCUSSION

Dr. Robert Klein, Pittsburgh: I think we are all very much in debt to the Salt Lake City group for all the fine work that they have done. This is the latest result of it. I think one word of caution must be raised, though, on the interpretation of the data from the patients with rheumatic fever.

In measuring the actual circulating level of hormone, and not the output per day, or at any given time, we measure the balance of the output of hormone less its breakdown and excretion. It may be that after a day of illness the degradation or the excretion of the hormone produced goes on at a more rapid rate, and actually the adrenal is still putting out increased amounts of hormone.

I admit that this is only an alternative possibility, but I think we must go carefully here.

Dr. Nathan B. Talbot, Chicago: This paper and the one which preceded it mark major advances in the study of adrenocortical function in children. The techniques used should clarify many problems which in the past have been the subject of guesswork rather than objective thinking.

I wonder whether the present authors have had an opportunity to show that the blood corticosteroid values obtained on healthy children are significantly higher than those obtained on hypoadrenocortical infants and children. If the answer is in the affirmative, it would support the idea suggested by urinary corticosteroid measurements that most pediatric patients are at least as capable of producing corticosteroids as adults.

Dr. Alfred M. Bongiovanni, Baltimore: We have treated nine patients having congenital adrenal hyperplasia with corticotropin (ACTH). In three of them we have had rises in the blood corticoids. I don't think this is necessarily in disagreement with what Dr. Kelley said. We think this is perhaps not an "all or none disease," but that there are various degrees of severity. Some patients can produce Compound F at low rates, and some perhaps cannot at all, and I just thought it might be worth mentioning that a few patients do respond.

DR. ALBERT DORFMAN, Chicago: I should like to question Dr. Kelley about only one minor point in all his very excellent data. That is, with respect to the very high values for salicylate intoxication—I wonder if there is any way of being sure whether or not any of the polyhydroxy compounds that are produced metabolically from salicylates are interfering in this method.

In some of the earlier work on urinary levels several years ago, many of us who were interested in the possibility that salicylates might stimulate the adrenal cortex were first sadly fooled by tremendous levels of corticoids apparently being excreted in the urine, which turned out to be just metabolic products of the salicylates.

DR. LAWSON WILKINS, Baltimore: I think this is extremely exciting work, and I wish to congratulate the workers. I think the work of Dr. Jailer has emphasized particularly that the disordered adrenal of the type discussed has difficulty in manufacturing normal hormone, Compound F, and that the synthesis of steroids is diverted to an abnormal pathway. I would be very much interested to know what abnormal steroids Dr. Kelley has found and which he feels may be responsible for the androgenic activity in this condition.

I am still a little concerned that in spite of the low levels of Compound F found (3 γ compared to a normal of 13) there are usually no symptoms of Compond-F deficiency, such as hypoglycemia, and the children respond to severe stress without harm.

DR. VINCENT C. KELLEY, Salt Lake City: I should like to thank all of the discussers. I will try to give you very briefly our thoughts with regard to the questions asked.

Dr. Klein suggested caution with regard to the interpretation of the results obtained in rheumatic fever. Certainly we are in agreement with that. I was careful to say two or three times during the paper that these were preliminary results. We do not feel that we have ruled out conjugation, destruction, or utilization in any of our studies so far, although in some cases we have ruled out urinary excretion as a factor influencing 17-hydroxycorticosteroid levels. In patients with early acute rheumatic fever urinary excretion is at least as great as in normal persons, and we feel that therefore secretion of 17-hydroxycorticosteroids by the adrenal is probably at least as great as normal. Certainly interference with conjugation or destruction may occur and play a significant role here.

I should like to thank Dr. Talbot, and will try to answer his questions. The reason that we don't have any typical hypoadrenal patients in our series is that since we have been working with the method, we have not had the occasion to study a typical one. On the adult service at Utah, circulating levels and responses in Addisonian patients have been measured. These levels have been low and the responses inadequate, although an occasional satisfactory response has been observed. As to the response of infants, we have only meager data, as I mentioned in commenting on Dr. Klein's paper. We have studied one infant in whom we thought we had found a rather tyipcal adrenal insufficiency. This infant had no eosinophile response to corticotropin (ACTH). However, we found that his 17-hydroxycorticosteroid level was elevated in response to corticotropin from a fasting value of 5 γ per 100 cc. to a two-hour value of 55 γ per 100 cc.

With regard to Dr. Bongiovanni's comment, we have done, as you saw, many response tests in a relatively few persons with congenital adrenal hyperplasia. The responses to corticotropin in our group have been consistently either zero or small responses averaging out to practically no response. However, we are not in a position to say that no patient with congenital adrenal hyperplasia will respond to corticotropin stimulation.

Dr. Dorfman brings up a very interesting question which I am unable to answer. In response to salicylate administration we have observed elevations of 17-hydroxycorticosteroid concentrations in guinea pigs and in normal human beings, but none in rheumatic-fever patients. I am unable to interpret these data.

I am likewise unable to answer Dr. Wilkins' question (Why don't patients with congenital adrenal hyperplasia have symptoms with reference to their hypoglycemia and low levels of Compound F?). However, this is not a unique situation. Any patient who has been treated with either cortisone or corticotropin for rather prolonged periods of time, for approximately 10 days after discontinuation of therapy has zero or near-zero levels of circulating Compound F. Yet these patients do not show symptoms of hypopglycemia or of Compound-F deficiency. Also an occasional "normal" person has a zero plasma concentration of circulating Compound F. These persons likewise have no symptoms of hypoglycemia or of adrenal steroid insufficiency.

Addison's Diseases Developing in a Boy with Hypoparathyroidism. Dr. C. Papadatos (by invitation) and Dr. Robert Klein (by invitation), Pittsburgh.

The patient, a 10-year-old boy, acquired Addison's disease over a two-month period while being treated for hypoparathyroidism. Although the diagnosis of hypoparathyroidism had only been made at this time, the history of alopecia went back several years. This is the third or possibly the fourth patient with such a combination of diseases that we have been able to find in the literature. The clinical features of the case will be presented and an attempt will be made to detail the progression of the Addisonian signs, symptoms, and related laboratory material.

DISCUSSION

Dr. Wallace W. McCrory, Philadelphia: The authors of this paper may be interested in a short report of another child with hypoparathyroidism in whom complete pancreatic insufficiency subsequently developed. We first saw this girl at 3 years of age, at which time she had classic findings of hypoparathyroidism. She was well controlled for about two years, after which time control was very difficult, and we found that deficiency of exocrine secretion of the pancreas had now developed, as demonstrated by duodenal enzyme analysis. This was followed in about six months by the development of classic signs of diabetes mellitus. The patient died about one year later. Prior to death, she did show some manifestations suggesting some adrenal cortex insufficiency, particularly of the salt-active steroids. Her condition was so complex, however, that this later condition was not clearly established. This patient would appear to be another example of the interesting association of multiple endocrine-gland insufficiencies manifested by patients originally having hypoparathyroidism.

Dr. Irvine McQuarrie, Minneapolis: We observed a similar case. It was a patient whom we had studied for quite a number of years, making mineral-balance studies and testing a number of the endocrine functions. The patient finally became somewhat better as regards the hypoparathyroidism. We had attributed his imporvement to our treatment. We gave no huge dose of vitamin D like this, but a low phosphorus and rather high calcium intake and maybe a little more than the normal requirement of vitamin D. He was really treated quite physiologically, so to speak, on the whole.

Addison's picture finally developed, and the patient died. That is why I mentioned it. This one seems to have returned to normal, largely. Our patient died, and Dr. Arild Hansen, being an "eager beaver" about such problems, went 125 miles to do the autopsy, at which he found the adrenals to be completely atrophied.

I believe that there is some, as yet, undiscovered interrelationship between the parathyroid and the adrenal glands which is well worth looking for by means of suitably designed animal experiments.

Dr. Harry H. Gordon, Baltimore: I had the opportunity to observe the patient in the case reported by Dr. Leonard. She was followed at the nursery and at Children's Hospital by Dr. Arthur Anderson because of hypoparathyroidism and convulsions and then at the New York Hospital, where for several years this was still the picture.

Then Addison's disease developed, and at this time her convulsions became much less frequent in number. She subsequently died, and my recollection is that in addition to the adrenal atrophy she had a lack of basophile cells in her pituitary gland.

Dr. Josef Warkany, Cincinnati: I have been interested in the relationship between Addison's disease and hypoparathyroidism because of an observation made many years ago at the Children's Hospital of Cincinnati. The case I refer to is that of a boy with Addison's disease whom we saw on many occasions. Our treatment was then inadequate, and the boy died. He did not have tuberculosis, and at autopsy no adrenal tissue could be found. The boy's sister had been observed by Dr. Guest previously because of convulsions and chronic hypocalcemia. She was transferred to an institution for epileptic children and finally died at home. No autopsy was made.

It seems that Addison's disease and chronic hypoparathyroidism have a common denominator and that these two conditions can be found dissociated within a family. A familial incidence was also observed in the cases of hypoparathyroidism and Addison's disease published from Boston

by Sutphin and co-workers and Talbot and co-workers. Here we may deal with a recessive hereditary condition. It is of interest that the family observed by us was of Italian extraction and, I think, one of the Boston families was Italian, too.

Dr. Lawson Wilkins, Baltimore: A practical point which I want to emphasize is the occurrence of photophobia in cases of hypoparathyroidism, a symptom which is not well known. In a group of five cases of hypoparathyroidism, which we have seen, photophobia was a presenting symptom in two. The children went to ophthalmologists over long periods. Conjunctivitis and keratitis developed, and they were suspected of having phlyctenular conjunctivitis. I think it is well worth determining the blood calcium and phosphorus in unexplained photophobia. With treatment, the photophobia disappears like magic as soon as the calcium reaches the normal level.

Dr. Henry L. Barnett, New York: I think that one must be very cautious in interpreting changes in calcium and phosphorus metabolism as an effect of Addison's disease in this patient because of the known long-continued action of large doses of vitamin D in patients with hypoparathyroidism.

Adult patients with postoperative hypoparathyroidism treated with large doses of vitamin D may show no return of the symptoms of hypoparathyroidism for many many months after discontinuation of the therapy.

I should like to ask one question: Did the authors consider the possibility of using the sodium salt of ethylenediamine tetraacetic acid to reduce serum calcium during the period of hypercalcemia?

Dr. Arild E. Hansen, Galveston, Texas: Dr. McQuarrie has made reference to the case studied by us. It might be of interest to point out that this child was primarily being studied to determine the effectiveness of pitressin in relation to the production of the hypoparathyroid type of convulsion. It was noted that over a period of some months when he was on a low-mineral diet he had convulsions precipitated by vasopressin injection (Pitressin), whereas when he was on a high-mineral diet he did not have convulsions. When our child did come back—he was no longer a child, something like 21 years or so—there was evidence of a full-blown Addison's disease. At this time there was no semblance of the previous manifestations of hypoparathyroidism; all the signs had disappeared.

Dr. C. Paadatos, Pittsburgh: I want to thank all the discussers of our presentation for making our paper look more sound and clear.

I would like to reemphasize one point. Here we have a patient with hypoparathyroidism who is getting 200,000 units of vitamin D. Toxic signs develop, and we are obliged to discontinue administration of vitamin D. At the same time Addison's disease develops. A month later, at the height of an Addisonian crisis and without vitamin D, he gives off large amounts of phosphate. We raise the question of whether that was a residual effect of vitamin D or was it due to his adrenal insufficiency, and thus an ameliorating effect of adrenal insufficiency? We cannot answer that question.

Point number two is that the values for Compound F with this patient were 0 to 5, and that probably might answer Dr. Talbot's question on the previous paper.

The Development of Goiters in Cretins Without Iodine Deficiency. Dr. Lawson Wilkins and Dr. George W. Clayton (by invitation), Baltimore.

Studies of the uptake of radioiodine reveal that in nongoitrous regions there are occasionally congenital cretins who have normal-size or enlarged thyroid glands capable of accumulating iodine normally. In these cases the deficient production of thyroid hormone is not due to lack of iodine or to the ingestion of goitrogenic substances. There is probably a defect in the enzyme systems of the gland responsible for converting iodine into thyroxine.

We shall report four cases of hypopthyroidism of this type. Two of these were in infants with thyroid glands of normal size. In a third patient a small diffuse goiter developed at the age of 6 years and in a fourth a large nodular adenomatous goiter developed at 8 years. The latter patient was thyroidectomized. The entire gland showed marked hyperplasia and in addition contained numerous encapsulated neoplasms of pleomorphic structure. This case was similar to those of four cretins with normal iodine uptake in whom huge nodular goiters

developed, which were described by Stanbury. All of our patients and those of Stanbury were either untreated or very inadequately treated with thyroid. It is probable that the failure to control the hypothyroidism led to excessive secretion of thyrotropic hormone, which caused hyperplasia and neoplasia.

DISCUSSION

DR. EABLE, Buffalo: I would like to report two additional cases of hypopthyroid disease with normal or high I^{131} uptakes, which appear to be similar to those described by Dr. Stanbury and Dr. Wilkins. These patients had typical clinical findings of cretinism. They were intolerant of thyroid in doses exceeding 0.15 gm. per day. Protein-bound-iodine determinations were less than 2 γ per 100 cc. However, in one patient the I^{131} uptake was 38% and in the other it was 45%.

I believe that these patients should be distinguished from the typical cretin, not because there is any difference in their management, but because the basic mechanism of this hypothyroid disease would appear to be different from the usual cretin. Awareness of this fact, and further observation of this type of patient may give us important clues to the further understanding of thyroid metabolism.

DR. BENJAMIN KRAMER, Brooklyn: I wonder whether I missed it, but what were the protein-bound-iodine values?

DR. LYTT I. GARDNER, Syracuse, N. Y.: The discussion of this very interesting form of cretinism enables us to draw a worth-while comparison of the genetic mechanism involved in this condition with congenital sporadic nongoiterous cretinism. It would appear from the few patients now known to have goitrous cretinism that we are quite likely dealing with a genetic recessive trait, since there are usually several affected siblings in each family. On the other hand there is no evidence available to indicate that the congenital sporadic nongoitrous cretin represents any known type of Mendelian inheritance. There is an increased incidence of thyroid dysfunction in the relatives of patients with this latter variety of cretinism, as Dr. Childs and I mentioned earlier, but the exact genetic mechanism has eluded us.

DR. ROBERT COOKE, New Haven, Conn.: The finding of a normal or increased mass of gland and normal radioiodine uptake would suggest possibly a rerouting of iodine into non-hormonal channels. In these cases the comparison of serum-precipitable iodine to butanol-extractable iodine, which may be closer to the true serum-hormone level, might be of benefit.

A few days ago such a difference was demonstrated by Dr. Crawford in cases of Hashimoto's struma.

DR. LAWSON WILKINS, Baltimore: I wish to thank the discussants, particularly those that pointed out some shortcomings in our study which I was trying to supress here.

I feel quite sure that if looked for, this type of hypothyroidism will turn out not to be exceedingly rare. This is a type of hypothyroidism quite distinct from the embryonic defect in development of the gland. It is exceedingly important to treat these patients adequately to prevent hyperplastic and perhaps neoplastic changes.

Dr. Kramer, I regret very much that we do not have values for protein-bound-iodine on these patients. Unfortunately this determination was not being done in our institution at the time.

Likewise, Dr. Cooke, it certainly is most important to study the plasma fractions of iodine in these cases. We wished to make such studies in the last case, but were just setting up the methods at that time. I hope we will have more cases and will be able to study the conversion rates of I^{131}, that is the ratio of total serum I^{131}, protein-bound I^{131}, and the butanol extract I^{181}.

Another study which someone should have accused me for not mentioning is that which Stanbury made in regard to the ability of potassium thiocyanate to release unbound iodine from glands such as these. In Stanbury's cases, at the end of 4 hours in most of the cases and in one case as long as 24 hours after the administration of radioiodine, potassium thiocyanate was administered and caused a marked release of the iodine from the thyroid glands. We tried this in several of these cases with negative results. The possible explanation of the difference in our results is that we were giving radioiodine intravenously whereas he gave it orally. Maybe that causes some difference in the binding.

Dr. Talbot's point about adolescent goiter is an interesting one. It is certainly quite true that the way to make an adolescent goiter decrease is to give thyroid. In many of these cases

the enlargement causes so little trouble that we have not bothered to treat them. In some of the larger ones, we have treated them largely with the idea of improving the cosmetic effect, but it is certainly conceivable that it might be important to supress the gland with thyroid therapy from the theoretical possibility that such a gland might undergo some adenomatous or more serious type of change.

Dr. Gardner's paper the other day indicated that in the athyrotic type of cretinism there is no significant familial tendency. However, there are two other groups of congenital hypothyroidism in which there is a marked familial tendency. One is the type of hypothyroidism just discussed in which the child is born with a normal-size thyroid which is unable to synthesize the hormone. In the other group which I did not discuss the child is born with an enlarged diffuse goiter —often two children in the same family—and mild degrees of hypothryoidism. I do not know the cause of this, but perhaps there is some maternal influence acting on the fetus.

Insulin Requirements from Infancy to Adulthood of Children with Diabetes Mellitus in Good Control. Dr. Robert L. Jackson and Dr. P. Tirumala Rao, Iowa City.

Analysis of data accumulated over many years from a group of diabetic children maintained essentially in physiological control yields important practical and fundamental knowledge of the disease. This presentation is concerned with the insulin requirements of such a group of diabetic children with the onset of disease at ages ranging from 1 to 15 years and the period of observation ranging from 3 to 20 years.

A pattern of exogenous insulin requirements is found which is interrelated with growth and development. The average insulin requirement from infancy to adolescence increases slowly or rapidly as a reflection of the growth pattern of the child. The insulin requirement of girls increases rapidly after 10 years, whereas the insulin requirement of boys increases rapidly after 12 years, concomitant with their respective prepubescent growth spurts. Subsequently, the requirements gradually decrease and become more constant as growth decelerates and adulthood is reached. Marked increases are observed during periods of physical or emotional stress, but the requirement quickly returns to the usual pattern when the stressful situation is removed.

Severity of disease as reflected by the exogenous insulin requirement is not related to the age of onset of the disease in early childhood. Comparison of the insulin requirement of an individual patient in good control with the range of values found in a group of well-controlled diabetic children gives some indication of the severity of the child's disease.

Knowledge of the range of insulin requirement provides an objective means of evaluating factors which influence the insulin requirement and the degree of control and may be helpful in differentiating types of diabetes in children. The data give us a better understanding of the pathological physiology of the disease and suggest that juvenile diabetics are producing small but varying amounts of endogenous insulin. The findings are in keeping with the data in the literature on the amount of extractable insulin from the pancreas of diabetic and nondiabetic children and the insulin requirements of adult patients with total pancreatectomy.

The study is based on the three-month-interval insulin and nutritional requirements of 48 children under continuous observation in our clinic. These patients have maintained essentially physiological control of their disease, and at the time of observation were free from known infections and emotional disturbances. All subjects grew normally. Such factors as the age of onset of the disease, sex, body build, and the interval between time of onset of the disease and the beginning of adequate management are evaluated.

DISCUSSION

Dr. George M. Guest, Cincinnati: I wish to congratulate Dr. Jackson on this important addition to our knowledge of juvenile diabetes. His careful compilation of data here presented offers a valuable basis for comparing observations similarly made on diabetic children treated in other clinics; and his design for statistical analysis will facilitate the work of all other investigators who wish to compare their data with his.

Practices in diabetic management in our Cincinnati Children's Hospital Clinic differ from those of the Iowa Clinic mainly with respect to the degrees of glycosuria deemed permissible and the day-to-day freedom allowed for variations in food intake. We agree, of course, that the maintenance of normal growth is the most important criterion of success, if a single one

can be chosen. On the basis of personal experience I concur with Dr. Jackson's main conclusion, that increasing exogenous insulin requirements reflect growth patterns and are most closely correlated with increasing body weight. I believe that the average daily insulin dosage employed in our clinic corresponds closely to the averages found by Dr. Jackson in his clinic among diabetic children of comparable age and duration of disease. Moreover, data I have collected from colleagues in a number of different centers indicate that no significant differences will be found between average daily insulin dosages employed in their respective clinics. As Dr. Jackson's graphs demonstrate, there is a considerable span covered by individual variations above and below the mean daily dosage at advancing ages. I cannot subscribe to the suggestion that "the insulin requirement of an individual patient . . . gives an indication of the severity of the child's disease." Insulin requirements in individual children may vary greatly from time to time with changing conditions of intercurrent infection, emotional stress, hormonal imbalance at the time of puberty, etc.; such factors may temporarily influence insulin action and dosage requirements without necessarily affecting the status of the disease itself.

It seems to me therefore unsafe to interpret any level of daily insulin requirements as an index of successful physiological control of the disease.

Dr. Julian D. Boyd, New Orleans: I would like to stress the value of the data which Dr. Jackson has presented and make three brief comments.

The first point deals with the predictable increase of insulin need as a concomitant of growth. It is important that the physician who is treating the diabetic child be familiar with this increasing need and that he explain it in advance to the patient so as to forestall the thought that the patient's diabetes is not being properly managed. We can expect insulin need to increase under standard conditions throughout childhood.

Secondly, clear distinction should be made between the dose of insulin which the physician may prescribe for the patient and the amount of insulin actually needed by the patient to maintain control of his diabetic state. The two amounts are not the same unless the criterion of dosage prescription is well defined and the degree of diabetic control is being measured through suitable laboratory procedures. The diabetic children from the Iowa studies have been treated with the objective of maintaining normoglycemia insofar as possible at all times; their insulin dosage therefore really portrays their true need under their current habits of life, as well as how such need can be determined with the means at hand.

My third point is supplementary to Dr. Jackson's report. In studies of similar nature, made by me about 20 years ago and dealing with a similar population of diabetic children, each child's progressive insulin requirement was expressed in terms of body weight and the glucose equivalent of his diet. Using such individual curves, it was noted that the total daily insulin requirement tended to increase abruptly under presumably similar conditions of living, this change occurring about nine months before the growth curve showed the prepuberal acceleration, well in advance of physical evidences of approaching puberty. Insulin requirements then would remain high well into the period of adolescence. Then the required dosage for a given dietary regimen would drop with equal abruptness from possibly 100 to 150 units to 35 to 40 units daily at a time when the patient had passed through the major physical and emotional adjustments related to adolescence. The constancy of insulin need seems to reflect the stability of the total endocrine pattern of the patient, and through related mechanisms it may reflect the stability of the emotional set.

Dr. Robert L. Jackson, Iowa City: I wish to thank Dr. Guest and Dr. Boyd for their discussion of our paper. In recent years Dr. Guest and I have had many discussions regarding the treatment of children with diabetes, and as our knowledge and understanding have increased, our differences have decreased.

I fully agree that the insulin requirement itself is a poor index to the severity of the disease, and consequently I used the term hypoinsulinism rather than the severity of the disease. The severity of the disease is particularly reflected by the tolerance of the patient to slight variations in insulin dosage, dietary intake, and physical activity, which in turn is reflected by the blood-sugar level, the degree of glycosuria, and the incidence of insulin reaction.

The most notable apparent effect of prolonged hyperglycemia is evidenced by the difference in response between patients who recently have become diabetic and those who have remained

glycosuric for some time before good control is attempted. The latter patients have a much narrower zone of stability and are definitely more difficult to control than patients whose disease was well controlled soon after the onset of the disease.

Patients who are maintaining a fair degree of control, that is, excreting minimal amounts of sugar in the urine, can grow normally. Normal growth does not preclude the development of degenerative changes, but when there is definite deceleration or stunting, degenerative changes develop earlier and progress more rapidly. Dr. Guest and I are interested in learning the truth and have little concern as to who is right and who is wrong. Long-term observations of our patients in varying degrees of control eventually should answer the question as to what constitutes adequate care of the child with diabetes mellitus.

Hypothermia in the Diagnosis and Treatment of Congenital Cardiovascular Anomalies.

Dr. Samuel Kaplan, Dr. Jares A. Helmsworth, Cincinnati, and Leland C. Clark, Ph.D., Yellow Springs, Ohio.

Infants and children with congenital cardiovascular abnormalities amenable to surgery are frequently in a poor general condition because of intractable heart failure or severe hypoxia. These patients are denied specialized investigations and surgical therapy because of the prohibitive fatality rate attending these procedures. Since anoxia is the underlying abnormal state in many of these infants, is seemed reasonable to attempt to decrease the oxygen requirements of the tissues temporarily while the special investigation or surgical therapy was being performed. Reduction in oxygen requirement was accomplished by inducing a hypothermic state in these patients.

In 23 infants between the ages of 1 to 10 months and in two boys aged 4 years, the rectal temperature was reduced to between 69 and 84 F. (20.6 and 28.9 C.). The procedures carried out consisted of the following: 13 angiocardiograms, 3 aortograms, 1 cardiac catheterization, 2 ligations of patent ductus arteriosus, 5 aortic-pulmonary anastomoses, 1 pulmonary valvulotomy, and 1 closure of a ventricular septum defect.

The method used to reduce the body temperature was to pack polyethylene bags containing ice around the patient. The time taken to reduce the body temperature to the above levels was from 18 to 80 minutes, the rate being more rapid in infants under the age of 2 months. After application of the ice bags, the initial fall of temperature was comparatively slow until a level of about 90 F. (32.2 C.) was reached, when it fell more rapidly. The temperature continued to fall for 3 to 5 degrees Fahrenheit after the ice bags were removed and then remained stable. When the diagnostic or surgical procedure had been completed, the patient was rewarmed by placing him in water at 104 F. (40 C.). A normal temperature was attained in about 30 to 60 minutes. In the majority of instances the temperature remained at normal levels after rewarming, but in two patients a pyrexia of 100 to 102 F. (37.8 to 38.9 C.) developed which lasted about 24 hours.

The pulse and respiratory rates decreased as the temperature fell. Usually the pulse rate at normal temperatures was between 160 and 200 per minute and fell to between 60 and 80 per minute at a temperature of 75 F. (23.9 C.). The respiratory rate also fell from between 40 and 60 per minute to between 16 and 30 per minute. Other findings during the hypothermic state were a decrease in intensity of cyanosis and a small fall of the blood pressure. The applications of ice bags did not produce irreversible changes in the skin, and muscle tone was unaffected. The changes noted in the electrocardiogram were slowing of the heart rate and prolongation of electrical systole. A small amount of anesthetic agent was required during the surgical or diagnostic procedures, as the low temperature did not produce sufficient narcosis. Similar reduction in temperature was carried out in puppies, where, in addition to the above studies, the cardiac output was measured.

These studies indicate that the temporary reduction of body temperature in infants and children with severe congenital heart disease considerably reduces the risk attending surgical procedures and specialized investigations.

DISCUSSION

Dr. John A. Bigler, Highland Park, Ill.: I want to congratulate the authors for their fine presentation, but I must state that I am somewhat awed by their courage. I don't think that any of us know what the optimal body temperature is under varying conditions in infancy

and childhood. I do know that by reducing body temperatures less radically than in the instances reported, somewhat the same results can be obtained. We have found that if the body temperature is reduced to 94 to 95 F. at induction of anesthesia, one can carry on the operative procedure for an hour to an hour and one-half without any more anesthetic. As soon as the body temperature rises to 97 F., anesthetic is again required.

We have also observed that in those children in whom the body temperature was below 97 F., postoperative resuscitation was not necessary in the operating room. I am talking about the very ill cardiac patient and other serious intrathoracic surgery patients. Postoperative resuscitation was frequently necessary when body temperatures were either normal or were somewhat increased.

We have also observed that during anesthesia most body temperatures tend to rise, except in the infant under 6 months of age, when it tends to fall. I think that the whole question of hypothermia is going to require a good deal more investigation. We are all accustomed to thinking that all persons should have a normal temperature. Recently, I have had two experiences with premature infants that were allowed to seek their own body temperature. The rectal temperature promptly dropped to between 89 and 91 F., and seemed to get along perfectly well.

The same thing happened to two other infants 2 to 3 weeks of age brought to the hospital in a very severe state of malnutrition, and dehydration, with body temperatures of 91 F. Allowing them to maintain their own body temperature apparently had no deleterious effect.

The term hypothermia covers a wide range of degrees between the accepted normal temperature and that point at which irreversible change incompatible with life takes place. Pediatrics will profit by further research on optimal body temperatures.

Dr. Forrest H. Adams, Los Angeles: I would like to ask the authors three questions. One is whether or not this procedure of hypothermia might be used routinely in surgery of cyanotic heart disease.

My second question is, has this type of anesthesia been used during other types of surgery? Likewise, has it been used in the treatment of other diseases that might benefit by lowering of the metabolic rate?

Thirdly, I would like to state that as to the effect of hypothermia on mentality, I believe some investigators using this technique have followed the patients with continuous electroencephalograms and have found no abnormality when they recovered consciousness. I wonder whether or not the authors have made any tests to determine the effect on the psyche, in other words, whether patients have been tested psychometrically before surgery and after surgery.

Dr. Helen B. Taussig, Baltimore: We have not had any experience in hypothermia; nevertheless I am extremely interested in the work. On the other hand, we have not refrained from testing any children with angiocardiography or aortograms because we thought they were too critically ill. If we felt they might be benefited by operation, we have not withheld surgery.

It seems to me that 1 death in 18 in dogs indicates that this treatment is quite as dangerous as the tests; indeed, I don't believe our accidents are anything like as high as that. I am sure they were under 5%, and I think under 2% even in critically ill children.

Dr. A. S. Nadas, Boston: I would like to ask the authors how they manage to keep the body temperature at the optimal level once it has been attained. What do they do so that it does not go below the desired level?

The second question I would like to ask is whether anybody has investigated the effect of hypothermia on the tendency to thrombosis that presumably exists in these sick cyanotic children.

Dr. Samuel Kaplan, Cincinnati: I would like to thank all the discussers for their comments and will attempt to answer their questions in the order that they were asked. I believe there is a big difference between the induction of hypothermia and the prevention of hyperpyrexia. Some years ago, Dr. Potts was impressed by the not infrequent occurrence of pyrexia in children during long surgical procedures such as in the treatment of tetralogy of Fallot. He instituted measures to attempt to keep the body temperatures in the low nineties. On the other hand, the object of our study was to attempt to decrease the general metabolic rate and oxygen requirements of the tissues by extreme hypothermia.

We have not used hypothermia routinely in all patients, since this is not necessary, as Dr. Taussig pointed out. There does remain, however, a group of patients who are so critically ill that in the past we have hesitated to carry out diagnostic or surgical procedures because of their prohibitive mortality. Angiocardiography, for example, which is relatively innocous for infants and children whose cardiac status is fair, becomes hazardous in these critically ill children. We believe that the use of hypothermia in such cases has enabled the patients to survive.

We have used hypothermia in only one infant with a noncardiac disease, i. e., with a tracheo-esophageal fistula. This patient's defect was repaired successfully while his rectal temperature was 69 F.

The intelligence and general neurological response of the patients have not been grossly affected, but the follow-up period has been short. Temple Fay used hypothermia in the treatment of neoplastic diseases in adults and children and, as far as I am aware, did not observe changes in the function of the central nervous system.

It is difficult to estimate the optimum level to which the temperature should be reduced, but the measurements of the heart and respiratory rates and duration of electrical systole are helpful. When the heart rate is between 80 and 110 per minute and the corrected Q-T interval above 0.42, the optimum temperature has probably been reached. When the cracked ice was removed from the patient, reapplication was usually not necessary, and some of the patients maintained a constant level of low temperature for up to two hours. We have not studied the problem of the increased tendency to intravascular thrombosis during hypothermia.

(To Be Continued)

SOCIETY FOR PEDIATRIC RESEARCH

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First Session

Monday, May 4

Etiologic Factors in Sporadic Cretinism: An Analysis of Ninety Cases. Dr. Barton Childs, Baltimore, and Dr. Lytt I. Gardner, Syracuse, N. Y.

Clinical data on 90 congenital sporadic nongoitrous cretins have been analyzed by the genetic statistical methods devised by Penrose and by Haldane. The Wilkins-Fleischmann series of cretins comprised most of the cases which were studied (*J. A. M. A.* **116**:2,459, 1941). Much of the data was obtained directly from the parents or by questionnaire. Comparison was made with a normal control group of 78 families from whom comparable data were elicited. The findings were as follows: 1. There was a significant familial incidence of thyroid disease, not necessarily cretinism. 2. There was no unusual incidence of consanguinity, and only two cretins had cretinous siblings. The latter findings argue strongly against the condition being a simple Mendelian recessive trait. 3. There were but two Negro cretins, although more than two-thirds of the patients came from Maryland and the District of Columbia. 4. There was a tendency for the cretins to be the offspring of older, multiparous mothers. 5. The cretins were significantly heavier babies at birth than were normal babies, and a frequency-distribution curve of the birth weights showed a bimodality which suggested two groups of cretins, one with relatively normal weights and the other with much greater weights at birth. Comparison with maternal age indicated that the heavier babies were the product of older mothers. 6. There was no seasonal incidence of the disease. 7. The male : female sex ratio was approximately 1 : 2, a previously described observation.

DISCUSSION

Dr. Edna H. Sobel, Cincinnati: I should like to ask Dr. Gardner whether he has data on the incidence of diabetes in the families of the cretins. In a much smaller series which Dr.

Nathan Talbot and I reviewed in Boston, we were impressed with the finding of as high an incidence of diabetes in the families of children with congenital hypothyroidism as of those with thyroid disease.

Dr. Lytt Gardner, Syracuse, N. Y.: When we compared the cretin group with the control group, there was no significant difference in any disease state that we investigated, except the ones mentioned.

Diluting and Concentrating Mechanisms of the Kidney in the Premature Infant. Dr. Philip L. Calcagno, Dr. Mitchell I. Rubin, and Dr. David H. Weintraub, Buffalo.

It is known that young premature infants are unable to concentrate urine to the same degree as adults. Several possible explanations have been advanced: (1) a lowered production, (2) a failure of the distal tubule to respond to the antidiuretic hormone effect, and (3) a lowered rate of solute excretion secondary to the lower glomerular filtration rate.

We have tested these hypotheses in five premature infants weighing approximately 1,500 gm. and varying from 5 to 28 days of age. Serial determinations with mannitol loading were made at different ages. In our infants a 25% mannitol solution was used, raising the plasma osmolarity 50 milliosmoles above the initial plasma concentration.

It was shown that (1) premature infants concentrate urine at high urine flows by reabsorbing a constant amount of water (maximum value, 2 cc. per minute per 1.73 sq. meters), which is less than half that of the adult, and (2) at low urine flows the significant factor limiting water reabsorption is the low osmotic U : P ratio characteristic for the dehydrated premature infant of 2.49, but which approaches the adult maximal osmotic U : P ratio of 4.00 shortly after birth. It was also shown that these premature infants were able to dilute urine comparable to that of the adult. Since the osmolar clearance of premature infants is less than one-half that of adults, less water was needed to reduce urine osmolarity to comparable low levels.

During mannitol loading, a rise in the creatinine : inulin ratio was observed from 1.18 to 1.90. Inulin clearances rose about 75%, and creatine clearances showed a rise of 140%. In these premature infants, sodium and chloride comprised a higher percentage of the osmolar load than was seen in adults. Potassium excretion did not follow patterns similar to those of sodium and chloride.

DISCUSSION

Dr. Solomon A. Kaplan, Cincinnati: Dr. Calcagno and his co-workers are to be commended on this fine piece of work. Studies carried out in Cincinnati on older children have also suggested strongly that there is no relationship between the rate of glomerular filtration (the factor responsible in a large measure for the magnitude of excreted load in these experiments) and the presence of a concentration defect.

The individual values for sodium excretion versus excreted load and chloride excretion versus load in older children and adults show some scatter, and I would urge that the values presented in this paper be compared statistically with the normal values before it is accepted that premature infants excrete larger quantities of electrolyte per unit of nonelectrolyte load than do older children. There is some doubt in one's mind that there will be a significant difference between the two groups when chloride excretion is examined in this way.

Dr. Henry L. Barnett, New York: In regard to the question which Dr. Kaplan mentioned of rate of excretion of solutes in these small infants, I should like to ask whether or not it is true that these infants are excreting solutes at a rate below that which is achieved by most older children and adults.

I should like to ask also whether this fact might explain Dr. McCance's observation that when loads of urea or sodium chloride were given to premature infants, instead of the urine flow increasing with a fall in total osmolarity, as in the adult, there is actually an increase in total osmolarity, without much increase in the rate of urine flow.

I am not sure whether Dr. Calcagno mentioned what type of milk his infants were receiving. This would affect their rate of solute excretion.

Dr. William M. Wallace, Cleveland: I am probably very old-fashioned in my thinking, but I should like to ask Dr. Calcagno whether he could discuss the following for us. I was brought up to believe that, thermodynamically, it took as much work for the kidney to dilute

the urine as to concentrate it. It seems to me that he has just shown us that this is not true. I wonder whether he could tell us why we should or if we must get away from a thermodynamic interpretation of how the kidney works.

DR. PHILIP L. CALCAGNO, Buffalo: With regard to Dr. Kaplan's first question, in calculating the load excretions, I think that I am fairly safe in saying that the solute excretions in premature infants are lower than those found in adults. Regarding the second point concerning the significance of excessive chloride loss, although the chloride data are not as striking as the sodium-excretion data, I think the tendency is in the same direction. Dr. Kaplan's question is a good one, and it may be that chloride excretions fall within ± 2 S.D. of the median line for adults. On the other hand, we have found, as I mentioned previously, that one patient whom we studied on two occasions did not show this tendency toward increased loss of sodium chloride. This greater loss of sodium per unit of load in the premature infant may be dependent upon variable circumstances in each infant.

With regard to Dr. Barnett's question about the differences in our data as compared with Dr. McCance's, you will remember that his data showed the newborn infants responded with a rise of the urine osmolarity with hypertonic sodium chloride and urea solutions. I think the differences between the data of Dr. McCance and our own may be that the babies studied by his group were not truly hydropenic. We proved to our satisfaction that the state of hydration of the body is an important factor in loading. A baby deprived of water for 12 hours and then given intravenous mannitol loading responded with a fall in the urinary osmolarity. After repeating the very same test and giving the baby 1 oz. (30 cc.) of formula two hours before we did this test, we found the urine concentration at this time to be low, and then the urine osmolarity rose with mannitol loading. We feel this indicates that the differences in the two responses could be explained by the state of hydropenia.

With regard to Dr. Wallace's question involving the work in dilution and concentration, I believe that this concerns thermodynamic interpretations, and I am not certain that I am willing to accept the implications of such calculations at this time. I will leave it at that.

A Study of the Outcome of Pregnancy in Women Exposed to the Atomic Bomb in Nagasaki. DR. JAMES N. YAMAZAKI, DR. STANLEY WRIGHT, and DR. PHYLLIS WRIGHT, Los Angeles.

A study was conducted in Nagasaki in 1951 to determinte the effects of the atomic explosion on fetuses in women who were in Nagasaki on Aug. 9, 1945. The outcome of pregnancy in women who were within 2,000 meters of the hypocenter is compared with that of a control group at 4,000 to 5,000 meters at the time of the atomic bomb explosion. Among the mothers within 2,000 meters in whom "major" signs of irradiation damage developed, the fetal and infantile mortality and morbidity was 60%. In contrast, the over-all mortality and morbidity of the fetuses and infants in the group without "major" irradiation signs within 2,000 meters and the control group were 10% and 6%, respectively. The mean height and head circumferences of the children born to the mothers with "major" irradiation signs were significantly smaller than those of the children in the control group. The evidence suggests that irradiation, either directly to the fetus or indirectly as a result of its effect on the maternal tissue, was of considerable importance in determining the outcome of the pregnancy.

DISCUSSION

DR. ROBERT MILLER, Rochester, N. Y.: Ionizing radiation from the atomic bomb produces the same qualitative effect as ordinary x-rays do. For those experimentalists interested in the effects of x-rays, the experience at Nagasaki and Hiroshima provides an opportunity to support the validity of their data obtained from laboratory animals. This paper does offer such support. So do other studies on cataracts, leukemia, hypoplasia of the dental enamel, etc., which have been carried out in Japan. These reports help to discredit some of the discreditors of radiobiologists.

The contentions of these investigators are of interest to the clinician, especially the pediatrician, not only because he can understand what has happened to the Japanese children but because he can understand perhaps a little better what might be happening in a lesser way to children as a result of the use of x-ray in routine medical practice.

Dr. Wright's study illustrates that new diseases do not occur as a result of radiation exposure, but only a change in the incidence of illness takes place. This indicates that the cause-and-effect relationship of x-rays and illness can be determined only by a measurement of the incidence of disease, and not by the strangeness of the disease.

The title of the paper includes the phrase "the outcome of pregnancy"; the outcome of pregnancy, the child, may not show the defects induced by radiation until the outcome of pregnancy grows to adulthood, when infertility is recognizable, a possible consequence as suggested by experiments on mice. Premature aging is another potential sequela of irradiation as shown by animal experimentation. Further study of the Japanese survivors may show this change. The outcome of pregnancy may be a person with defective germ plasm. Experiments on fruit flies and mice indicate that this abnormality may take generations to show itself clinically. So all the diseases involved in the outcome of pregnancy may not be known for many years.

Dr. Carl H. Smith, New York: I should like to know whether there was an opportunity to follow the children of exposed mothers for any appreciable time to determine the development of major blood disorders involving one or more of the principal cell series. If so, were they related to a particular period of pregnancy?

Dr. Stanley Wright, Los Angeles: Hematological observations were made on all three groups of children, and there were no significant differences among any of the groups.

With respect to the trimester of exposure, we could not find any significant difference, whether the exposure had been in the first, second, or third trimester. There was some suggestion that neonatal and infant deaths were somewhat increased if exposure occurred in the latter part of the second or third trimester in the group with "major signs"; however, these results were not significant.

Dye-Dilution Curves and Cardiac-Output Determinations in Newborn Infants. Dr. Klara J. Prec, and Dr. Donald E. Cassels, Chicago.

The pattern of dye-dilution curves and the cardiac output was studied in 28 healthy newborn infants during the first 48 hours of life by the method of Wood and his associates. A Brush recorder was used in conjunction with a Wood earpiece oximeter for the continuous recording of the dilution pattern of Evans Blue Dye (T 1824) following the injection of this dye into the umbilical vein. The amount injected varied between 0.4 and 0.5 mg. per kilogram of body weight. The umbilical vein was chosen for the injection because it permitted infants to be studied under ideal basal conditions while asleep and while breathing 100% oxygen. Blood samples (5 cc.) were drawn before and after injection of the dye, and a Coleman spectrophotometer was used to determine the amount of dye in the latter. The values obtained were used to determine the mean concentration of dye during its initial passage through the ear, and the cardiac output was then calculated by the Hamilton formula.

Four different types of dye-dilution curves were observed in these infants. Two of these were considered to be normal curves which differed in contour because of higher and lower cardiac outputs. The other two types are definitely abnormal in shape. One had the appearance of curves associated with left-to-right shunts and was characterized by a relatively small peak concentration and prolonged disappearance time. The other type was composed of a small shallow primary curve followed by a much deeper recirculation curve. Only 36% of all infants studied had normal curves, and these occurred most frequently in infants older than 15 hours. In contrast, most abnormal curves were found in infants under 15 hours of age. These abnormal curves were probably caused by an open fetal channel, most likely a patent ductus arteriosus. Our findings suggest that the ductus arteriosus does not close immediately after birth, but may remain open for as much as 15 hours or longer. The cardiac ouput and cardiac index were calculated in infants with normal dye-dilution curves. The mean value for cardiac output was 540 cc., which is in close agreement with values estimated by a number of investigators on the basis of theoretical considerations. The mean cardiac index was 2.5.

DISCUSSION

Dr. Nelson Ordway, New Orleans: I am much intrigued with the explanation of the probable left-to-right shunt which exists in the first few hours of life. While the situation is by no means anatomically comparable to that which was reported here two years ago in

transposition of the great vessels, in the latter the classic form of shunt appears to be from left to right through the foramen ovale, even though at postmortem examination the foramen ovale appears anatomically normal. I wonder whether also in normal infants the shunt could not occur from left to right in the newborn period.

I wonder if Dr. John Lind is in the audience and would care to comment on this paper, based on his observations of dye flow.

DR. KLARA J. PREC, Chicago: I was greatly interested in the comments about the angiocardiographic findings in newborn infants. We would have liked to do angiocardiography ourselves but found it impossible to do on healthy infants because of the inherent risk of the procedure and therefore the necessity of getting permission from the parents.

As far as the left-to-right shunt through the foramen ovale is concerned, we thought this was unlikely because of the magnitude of the shunt found in these infants. Judging from our experience with older children with congenital heart disease, left-to-right shunts which give rise to this type of curve are always shunts of a larger degree. Because of the position of the valvular fold guarding the foramen ovale and the relative pressure relations of the right and left auricles generally assumed, we thought it unlikely that a large shunt through the foramen ovale could occur under normal conditions. However, we may be entirely wrong about this.

In regard to a right-to-left shunt through the foramen ovale, we have found some evidence for this too. In a few of the normal curves the appearance time of the dye was between one and one and one-half seconds. Such a short time between injection of the dye into the umbilical artery and its appearance at the ear seems only possible if the dye did not go through the lungs, so that apparently most of the dye went through the foramen ovale to the periphery.

As far as the follow-up of individual infants goes, we are unfortunately unable to repeat injection of Evans Blue Dye (T 1824) in amounts necessary to obtain satisfactory curves. This dye stays in the circulation for over a week, and repeated injection would make the infant blue, which would be difficult to explain to the parents of a healthy newborn infant.

DR. FORREST H. ADAMS, Los Angeles: I believe the implication as the result of this work would be that the method could be used in studying heart disease in older infants and children. Have the present authors made such studies, and if so have longitudinal studies been made in the same patient over a period of days, months, or years?

I should also like to know how accurate the authors feel the method is in determining the actual amount of shunt.

Studies on Immunity to Streptococcal Infections in Man. DR. LEWIS W. WANNAMAKER, Cheyenne, Wyo., DR. FLOYD W. DENNY, DR. WILLIAM D. PERRY, DR. ALAN C. SIEGEL, and DR. CHARLES H. RAMMELKAMP, JR., Cleveland.

Antibody to the type-specific M protein has been shown to be responsible for immunity to streptococcal infections in animals, but its importance in men has not been determined. The present study was designed to evaluate the role of type-specific bacteriostatic antibodies in man's resistance to infection with homologous and heterologous types of streptococci.

The spread of Group A streptococci was closely followed among population groups totaling 131 persons in whom type-specific antibodies had previously been determined. The risks of acquiring streptococci were compared in persons with and without specific antibody to each type. The presence of type-specific antibody did not seem to influence the transitory acquisition of streptococci of the same type. Such acquisitions occurred in 23% of men with specific antibody to the type acquired and in 21% of men without specific antibody to that type. In contrast, the persistence of organisms and the incidence of clinical and subclinical infection were strikingly influenced by the presence of type-specific antibody. Parasitism or infection occurred in 13% of persons without specific antibody to the type acquired and in only 2% of persons with such antibody ($P = 0.001$). The presence of type-specific antibody had no effect on either acquisition of or infection by heterologous types of streptococci.

These observations not only indicate that immunity to streptococcal infection in man is chiefly type-specific in nature but also demonstrate that there is little heterologous immunity. If a polyvalent vaccine can be devised which results in the development of type-specific antibodies, it may prove useful in the prevention of streptococcal infections.

DISCUSSION

DR. ALFRED L. FLORMAN, New York: I think that the presence of streptococci in the throats of patients who have circulating homologous antibody is interesting. It might be pertinent in this connection to recall studies done by Francis a number of years ago with antibodies to Hemophilus influenza type A. He showed that the titer of influenza antibody in the nasal secretions was approximately one-tenth to one-twentieth that found in the circulation. I should like to know whether such quantitation was done in the present study.

DR. FRANCIS F. SCHWENTKER, Baltimore: One of the problems in epidemiological work on streptococcal infections has been our inability to prove that a person has actually had an infection due to the particular strain or type isolated from the throat. This paper has given information that it is now possible to do this. In our work at the Bainbridge Naval Training Station in the last war we attempted to show type-specific immunity by the use of complement fixation tests using purified antigens. We found that the sera of adults reacted to many different M proteins. On the other hand, the sera of infants generally failed to react. We interpreted this as evidence that a person develops immunities against these types by successive infections with various types of streptococci.

My question to Dr. Wannamaker is whether he considers such type-specific immunity to be long-lasting. Our opinion was that it was relatively short—a matter of several months.

DR. HORACE L. HODES, New York: I should like to ask Dr. Wannamaker a question on a point which was not made clear because he was pressed for time. I should like to know whether the soldiers were examined before their group got together, or whether they were studied after they had been together for a long time. It seems to me that if he demonstrated antibody in these men as they came together, rather than after they had been passing streptococci around for a while, his evidence would be strengthened. If it were not done in this way, he may have selected people who were immune on some basis other than type-specific antibody.

DR. LEWIS W. WANNAMAKER, Cheyenne, Wyo.: I should like to thank the discussers for their comments. In answer to the first question, we have not tried to demonstrate the presence of type-specific antibodies in the secretions of the nose or throat. To my knowledge, that has not been attempted. We did try to quantitate their level in the blood, but it is difficult to do precisely, and the best one can do is to say that a lot of antibodies, or very few, or none are demonstrable.

In answer to Dr. Schwentker's questions, some of these persons did have antibodies to more than one type of Streptococcus, but the risks were calculated independently for each type.

With regard to his question as to the duration of these antibodies, the evidence is not conclusive. However, our experience over the past five years has indicated that in many instances these antibodies last for a fairly long period of time—probably a matter of years.

In answer to Dr. Hodes's question, persons in the population at risk were classified by type according to the initial presence or absence of antibodies to this type. At the beginning of the study cultures were done by the Pike technique three times during one week to make sure that the men were not harboring streptococci at this time.

Excessve Intake of Vitamin A During Pregnancy as a Cause of Congenital Anomalies in the Rat. DR. SIDNEY Q. COHLAN, New York.

During the course of an investigation of the toxicity of vitamin preparations it was noted that abnormal offspring were produced when large amounts of vitamin A were fed to a pregnant rat. Preliminary data of an investigation undertaken to study this phenomenon is presented.

Mature female rats of the CF Wistar strain weighing 150 to 200 gm. were mated to males of the same strain. The experimental groups were fed an aqueous preparation of vitamin A containing 50,000 I. U. of vitamin A per cubic centimeter dispersed in a sorethytan-monooleate-and-water diluent. Control groups were fed an equal volume of the diluent. All feedings were by intubation, and pregnancy was allowed to continue to an estimated 21-day gestation. Offspring were delivered by section and immediately fixed in formalin for subsequent inspection for gross abnormalities and histologic study.

A marked decrease in the ability of pregnant rats to carry litters to term resulted when 35,000 I. U. of vitamin A was given daily from the 2d, 3d, or 4th to the 16th day of gestation.

Of 100 mated rats in the vitamin-A-fed group, 10 carried litters to term, a successful pregnancy rate of only 10%; whereas in the control group of 50 diluent-fed mated rats, 44 carried litters to terms, a successful pregnancy rate of 88%.

Of much greater significance was the incidence of congenital anomalies in the litters of the vitamin-A-fed group. Of 74 offspring obtained in 10 litters, 39 exhibited a gross anomaly in the development of the skull and brain which can best be described as an "exencephaly." Through a defect in the skull of varying size most of the forebrain was extruded to the surface of the head. Other anomalies, such as cleft palate, macroglossia, shortening of the mandible and maxilla, and gross eye defects, were also observed either alone or associated with the cranial deformity. Statistical incidence and detailed morphology of these malformations await histologic study.

In order to ascertain the minimal daily vitamin-A intake and the critical time of administration necessary to induce gross anomalies, several experiments were undertaken varying both the dosage and the period of vitamin-A intake during gestation. The results of this investigation would indicate that 25,000 I. U. of vitamin A fed daily to pregnant rats from the 7th to the 10th day of gestation will produce a consistently high incidence of gross abnormalities. In the control animals, 70 mated rats yielded 557 young, none of which exhibited any gross abnormality.

Though it is not intended in view of species and dose differentials to relate these observations to human malformations, the long-term results of these experiments with vitamin A, as well as the projected study of the other vitamins, either singly or in multiple preparations, may dictate more caution in the indiscriminate use during pregnancy of vitamin supplementation far in excess of human requirements.

DISCUSSION

DR. JOSEF WARKANY, Cincinnati: I am very happy about these experiments. They seem well controlled and clear cut, and I cannot see any fault in them.

May I ask one question? Has Dr. Cohlan any idea as to whether or not the vitamin A gets through the placenta?

DR. PHILIP ROTHMAN, Los Angeles: In view of the evidence that increased vitamin A stimulates the cells of the choroid plexus to produce an excess amount of cerebrospinal fluid, I wonder if Dr. Cohlan examined the choroid plexus and if the cells were hyperplastic.

DR. SIDNEY Q. COHLAN, New York: I should, of course, first like to thank Dr. Warkany for his very kind remarks, inasmuch as this problem has interested him for many many more years than I have been working on it.

As far as the first question about the choroid plexus is concerned, the histological study of our specimens is not yet available, and we expect in the future, of course, to report upon what we find in the various organ systems.

As for transplacental vitamin A, several years ago, in collaboration with Dr. Lewis, we ran an experiment in humans, in which we found that very very large amounts had to be given to the mother just before delivery to produce any significant rise in the newborn infants.

I am now working on a project of transplacental vitamin transfer, and I have found that with doses as given there is an appreciable increase in the vitamin-A content of the entire fetus, which increases as the fetus grows older. In other words, in the 8, 10, or 12-day fetus, there is hardly any increase, in spite of the fact that large amounts are given. But as the fetus gets older, I am able to detect a quantitative increase in the transfer of vitamin A from the mother to the fetus; but in spite of this, it is very very small. The entire fetus picks up approximately 6 to 7 units of vitamin A after the mother may have been given over a period of time well over 200,000 units.

The Association of Escherichia Coli Serogroup 0111 with Two Hospital Outbreaks of Epidemic Diarrhea of the Newborn in New York State During 1947. DR. ERWIN NETER, Buffalo, DR. ROBERT F. KORNS, and DR. RAY E. TRUSSELL, Albany, N. Y.

The association of certain serogroups (0111, 055, 026) of Escherichia coli with epidemic diarrhea of the newborn and infectious gastroenteritis of infants has been established by British

investigators since 1945. In the United States, these organisms have been isolated from patients with epidemic or sporadic diarrheal disease since 1950. This report summarizes the results of an epidemiological and bacteriological study of two hospital outbreaks of epidemic diarrhea of the newborn which occurred in two cities in New York during 1947.

The first outbreak took place between July 29, 1947, and Aug. 29, 1947, and involved 57 recognized cases (fatality rate 31.6%). The second outbreak occurred from the end of 1946 to October, 1947, and involved 33 (2.9%) of 1,118 full-term infants and 27 (31%) of 87 premature infants, the fatality rates being 6% and 37%, respectively. Fecal specimens from seven patients (five fatal cases) were kept frozen at a temperature of —40 to —70 C. for five years. Bacteriological examination in 1952 revealed that all specimens harbored Esch. coli 0111 and that this serogroup represented more than 95% of all coliform colonies obtained on primary plating. Attempts by two of us (R. F. K. and R. E. T., in collaboration with I. Gordon and H. S. Ingraham) to reproduce the illness in human volunteers by feeding these same fecal specimens from both outbreaks were unsuccessful. It is concluded that in the United States, as in Great Britain, Esch. coli serogroup 0111 was associated with at least two outbreaks of epidemic diarrhea of the newborn as early as 1947.

A study of a third and mild outbreak was made in a maternity hospital on Oct. 28, 1948, on six infants with diarrheal disease and on eight healthy infants and revealed that none harbored any of the above mentioned serogroups of Esch. coli in the feces. Esch. coli was present, but no single serogroup was common to all infants or even to all ill children.

The hemagglutination test for the demonstration of Esch. coli antibodies will be described and its sensitivity compared with the conventional bacterial agglutination test.

The Treatment and Prevention of Epidemic Infantile Diarrhea Associated with Escherichia Coli 0111 by the Use of Chloramphenicol and Neomycin. Dr. Warren E. Wheeler and Dr. Bertha Wainerman, Columbus, Ohio.

This report deals with the results of antibiotic treatment of patients involved in an outbreak of infant diarrhea in the wards of a general children's hospital. The outbreak lasted two months, involved 27 infants (6 infants acquired their infection outside the hospital and 21 acquired intrahospital cross infections) and was associated with the presence of a specific serotype of Escherichia coli (0111, 8$_4$) in the stools. The disease was characterized by its great severity in the very young infant, by a tendency to clinical and bacteriologic relapse, and by its high contagiousness.

Cross infection was common. Of exposed babies in the diarrhea unit, 58% of those below 2 months of age, 35% of those 2 to 5 months of age, 14% of those 5 to 12 months of age, and none of those 1 to 2 years of age acquired the infection. The reason for the great transmissibility probably lies in the preponderance of the pathogens in the stools. Nine of the adult hospital personnel became asymptomatic carriers, including the three porters who cleaned rooms in the affected wards.

The recognition of Esch. coli 0111 in stool cultures depends on the trial agglutination on a slide with rabbit serum prepared against the live organism. Consequently, one must be aware of the possibilities of the infection and look for it specifically to detect it.

Treatment of the patients with chloramphenicol was effective early in the outbreak in reducing the toxicity of the disease and in limiting the duration of the diarrhea, but in treated patients there was often an emergence of chloramphenicol-resistant strains of organisms. An attempt to prevent the spread of the epidemic by prophylactic administration of the drug failed, and in nearly every instance the organism recovered from these cross infected patients was chloramphenicol-resistant.

Neomycin was equally effective in the treatment of patients with the disease and was followed in no instances by emergence of neomycin-resistant strains of organisms. The outbreak ceased rather promptly when all patients were treated with neomycin and when adult hospital personnel who were found to be carriers of the organisms were discovered and also treated with neomycin. In contrast with reports of other outbreaks of diarrhea associated with this organism, our mortality was zero.

DISCUSSION

DR. ROBERT KLEIN, Pittsburgh: We have had clinical experience similar to that described by Dr. Wheeler. We have had 41 children with this organism cultured from the stools; 20 had no clinical symptoms. We have been singularly unimpressed with the results of treatment with chloramphenicol, polymxin, and in one case oxytetracycline (Terramycin).

The organisms disappear from the stool, but we see no effect on the clinical course, and the number of relapses seems to be about the same. The length of time in the hospital hasn't varied. Some of our children have got well and apparently have not had relapses over a period of a month or so, even though they still had the organism in their stools.

We produced a very neat outbreak in a small nursery when we sent one of our patients to that nursery just before the outbreak occurred on our regular infants' floor. We had 10 newborn infants, who comprised the whole nursery admitted to our service, all with this organism, four in the nose and throat, and all in the stools. We have had no experience with neomycin. We had three deaths among the 10 children in the newborn nursery.

DR. HORACE L. HODES, New York: First, I should like to say that we are very much indebted to Dr. Wheeler and Dr. Neter. They have accomplished two things which have done a great deal to clarify a rather confused picture. One has to do with the antibody technique. I think it is worth noting that the English workers have failed almost entirely to show an increase in the titer of antibody among infants presumed to be infected with the types of Esch. coli bacilli under consideration. The other observation of great importance is their demonstration of the fact that when these cultures were fed to infants, some cases of diarrhea were produced.

There are a number of questions still remaining. In considering the whole story of the evidence concerning the role of Esch. coli in the production of diarrhea since Theobald Smith's experiments with calves, in 1923, it seems to me fairly certain now that at least some types of these organisms can and do produce diarrhea and epidemics of diarrhea. One of the unanswered questions concerns the point that there have been only 4 types under suspicion of producing diarrhea out of 111 or so possible types.

Another curious thing has to do with the production of this type of diarrhea in newborn infants. It implies that antibody from the adult does not get over to the newborn infant in great quantities, or that there is no such antibody widespread in the adult population, perhaps because it is transient.

I think that experiments which we are now conducting dealing with the presence of antibody in gamma globulin and in the blood of mothers as compared with their newborn infants may yield interesting data on this point in the next year or two.

Dr. Wheeler certainly did obtain better results with neomycin than he did with chloramphenicol, but I don't think that he meant to imply that this will always be the case. I believe that in vitro sensitivity tests should be set up when we are dealing wih these organisms, because we shall probably find that there is great variation in sensitivity among various strains of Esch. coli to particular antibiotics.

DR. STEWARD CLIFFORD, Brookline, Mass.: I am disturbed by the epidemiological implications of Dr. Wheeler's paper. The spread of this organism implies that there has been a contact between the rectum and the oral cavity. I should like to ask if Dr. Wheeler was satisfied that major routes for the spread of infection had been blocked; were the formulas terminally sterilized by autoclaving, were approved methods of hand antiseptic used, and were masks used by the staff caring for these babies?

DR. NELSON ORDWAY, New Orleans: Dr. Klein, in commenting on these papers, pointed out that in his experience, if I interpret him correctly, approximately half of a nursery population that harbored these organisms had the disease.

I raise this point, which is also in line with Dr. Clifford's comment, because, for the past several years, Dr. Watt and his workers have been following the intestinal flora of premature infants in our large nurseries in Charity Hospital of Louisiana at New Orleans.

During these years we have been fortunate enough not to have had anything which might be called epidemic diarrhea of the newborn. There have been occasional sporadic cases of diarrhea. During all this time, there is an ebb and flow of organisms which seems to be char-

acteristic for the particular period. Proteus, for instance, begins to appear, then becomes the predominating organism in infant stools, and then subsides and its place is taken over by Pseudomonas or a paracolon type, and this sort of ebb and flow continues without any relationship to the presence of these sporadic cases of diarrhea.

Is it possible that the 0111 is doing this? If, for instance, we had had an attack of epidemic diarrhea of the newborn during one of the phases of prevalence of Proteus, it might have been tempting to say it was Proteus which was causing the attack.

Incidentally, we think our technique is reasonably good, and yet the anus-to-mouth contacts suggested must, of course, exist with us. It is interesting that the longer an infant stays in the premature nursery, the more likely he is to show in his stool culture what we call the typical organism of the moment.

DR. MYRON E. WEGMAN, Washington, D. C.: I should like to comment on the matter of the ease of identification of these organisms. Some of the studies which have led to a better understanding of the broad epidemiology of shigellosis and salmonellosis depended on prompt identification of suspected organisms from the original culture plate. The most striking errors resulted from failure to pick enough colonies for the further identifying procedures. In picking coli colonies, furthermore, one does not have the advantage of the primary color differentiation on the basis of lactose fermentation.

Has the practicability of identifying these strains of coli organisms been measured against the effort needed if one were reviewing a great many plates such as is necessary in a community epidemiologic survey? For example, Dr. Wheeler mentioned adult ward helpers in whom the organisms were discovered; how many colonies had to be investigated on each plate to detect these presumed carriers? In some of our studies in New Orleans there has been a direct and continuing relationship in that the more colonies picked, the more plates eventually positive for coli 0111. To make deductions concerning the significance of presence of these organisms, it will be necessary to culture family contacts and supposedly normal persons in large number. In view of the variability of per cent positive according to numbers of colonies picked, is the technique presently developed both feasible and practical in this sense?

DR. ROLAND B. SCOTT, Washington, D. C.: I have two questions in regard to the adult carriers who worked in the newborn area. Were they initially contaminated by the infants with the organisms under study or vice versa? How do you explain the apparent inconsistency between the asymptomatic carrier state in some of the personnel (nurses, porters, etc.) and the development of diarrheal symptoms in other adults who were fed the same micro-organisms experimentally?

DR. ERWIN NETER, Buffalo: I am very grateful to the discussers, and I will try to answer a few of the problems very briefly.

Dr. Hodes made some very important comments. Why only four serogroups of Esch. coli have been associated with epidemic diarrhea remains a moot question. It is likely that other serogroups may be encountered in the future which are associated with this disease. In turn, we may ask the question why only a few types of Group A hemolytic streptococci have been found to be associated with glomerulonephritis. It is obvious that as yet we do not know the mechanism by which one and not another serogroups of Esch. coli may be capable of producing diarrheal disease. It is equally clear that the characteristics, such as lactose fermentation and indole formation, which enable the bacteriologist to differentiate between salmonellae and escherichiae are mainly indicators for identification rather than the factors which determine pathogenicity.

Regarding the presence of Esch. coli antibodies in the population, we have examined, by means of the Esch. coli hemagglutination method, a large number of serum specimens from adults and children and have found group-specific Esch. coli hemagglutinins in the majority of sera. The question arises as to whether or not there is a transplacental transfer of these antibodies and whether the presence of such antibodies is related to resistance to infection with the homologous serogroup of Esch. coli. In outbreaks of epidemic diarrhea of the newborn infant, not all exposed infants acquire the disease. Studies are now in progress to elucidate this question.

The question has been asked whether Esch. coli 0111 is just an indicator for the spread of micro-organisms in nurseries or families without being an etiological agent. The evidence suggesting that this serogroup of Esch. coli is at least partly responsible for the disease is as follows: 1. In a given epidemic, this serogroup is present in the majority of affected infants. 2. The serogroup is usually the predominant coliform organism in the feces of such patients. 3. This serogroup of Esch. coli is but rarely found in healthy infants, children, and adults. 4. It has been shown that feeding of this serogroup of Esch. coli to infants and adults may produce diarrheal disease. 5. After ingestion of large numbers of Esch. coli of a serogroup associated with epidemic diarrhea of the newborn adults develop specific bacterial agglutinins and Esch. coli hemagglutinins. Such an antibody response did not occur in volunteers who ingested large numbers of a "normal" strain of Esch. coli. We are now studying the hemagglutinin response of infants suffering from diarrheal disease associated with certain serogroups of Esch. coli.

It is likely that nurses do not readily acquire the infection even when exposed to these serogroups of Esch. coli, since adults appear to be more resistant than infants. Large numbers of Esch. coli were required in the studies of Dr. Ferguson to produce diarrheal disease in adult volunteers.

Finally, regarding the identification of the serogroups of Esch. coli, thus far at least antigenic analysis is indispensable. We have been fishing from each specimen at least five typical Esch. coli colonies. It would be of great help if a differential culture medium were available on which "normal" serogroups of Esch. coli grow differently from those associated with epidemic diarrheal disease. Sorbitol agar may at least partly fill this need.

DR. WARREN E. WHEELER, Columbus, Ohio: I also wish to thank the discussers for their comments. It is obvious that this is not a cut-and-dried proposition, and long arguments could ensue between somebody who wanted to argue that this had no relationship to the diarrhea and those of us who have become impressed with it.

The thing that impressed me the most was, in our wards where we were conducting bacteriologic controls on our nondiarrheal patients, where we had negative cultures from some of those babies day after day that stayed healthy or stayed in a state recovering from their original diarrhea, to have the resident appear in our laboratory one morning and say, "My gosh, you have got a positive culture." And they say, "The baby went to pot last night." Sure enough, our culture on that particular day would be almost a pure culture of this organism.

There is no doubt in my mind but what observing case after case of that sort where you knew beforehand that your cross-infected babies had been culturally negative and had become culturally positive at the same time that severe acidosis, dehydration, and diarrhea had really developed, is the most important line of thought in our operation.

Of the nine carriers, two were symptomatic. They did have diarrhea and upset stomach. The rest of them were negative and asymptomatic.

Dr. Scott, the carriers were located in the epidemic, and we presume they got the disease from the babies. In the first place, we have no way of telling how many babies were infected.

In answer to Dr. Wegman's question, unless differential media are developed to highlight these pathogenic colonies, it is going to be a big problem, because, although the freshly diarrheal baby may have a pure culture of these organisms in his stool, in the carriers, convalescent babies, and those babies under treatment with antibiotic drugs the colonies may be in the minority, but they are there.

As to the number of colonies which should be investigated, we might say 15. Dr. Neter says five. It is a tremendous cost of serum and time to do that sort of thing, and it is not practical on a large scale.

As for Dr. Clifford's comments, I think they are the most pertinent of the lot, if this organism is this prevalent in the stools, what kind of technique can you possibly develop to stop an epidemic when the majority organism in the stool is pathogenic? In our situation, our milk is autoclaved, and we tightened up on the technique the best we could. Our cross inspections continued to appear. Little babies seem to me to be far more susceptible to the disease. They apparently require a smaller inoculum to develop it. For that reason, I think that prompt detection of these organisms and the reduction in the number of pathogenic organisms in the stools to practically zero should be a mainstay in the control of these outbreaks.

Fetal and Adult Hemoglobins in Premature Infants with Observations on the Mechanism of the Anemia of Prematurity. Dr. Irving Schulman, and Dr. Carl H. Smith, New York.

The purpose of this investigation was to study the quantitative aspects of hemoglobin synthesis and hemoglobin degradation in premature infants, with particular reference to the implications of these changes in the pathogenesis of the anemia of prematurity. Since prenatal and neonatal life are characterized by the presence of two types of hemoglobin, fetal and adult, we were interested in the significance of both.

As the initial phase of the study, the percentage of fetal hemoglobin in the cord blood of 96 normal full-term infants was determined by the method of alkali denaturation. In full-term infants a wide range of initial fetal hemoglobin was encountered, from 54% to 89%, with a mean of 71%. Because of the wide span, it was decided to study only those premature infants with birth weights of 2,100 gm. or less. The group consisted of 33 babies of whom 2 were under 1,000 gm., 14 between 1,000 and 1,500 gm., and 17 between 1,500 and 2,100 gm. In the premature group the range of initial fetal hemoglobin percentage was much narrower, from 68% to 89%, the mean at 82%. It was of interest that even the smallest infants had at least 10% of the adult hemoglobin at birth, indicating that this type of hemoglobin probably begins to be formed before the third trimester of gestation.

Studies of the changes in percentage of fetal hemoglobin with time indicate that a fairly uniform pattern exists in all weight groups. This consists of an initial period of 3 to 5 weeks during which the percentage of fetal hemoglobin falls very slowly, a second period of fairly rapid fall, and a third period when the rate of fall again decreases. The presence of significant amounts of fetal hemoglobin at 120 days, the normal life span of the erythrocyte, indicates that some fetal hemoglobin must be formed postnatally. Practically all fetal hemoglobin had disappeared by 8 to 9 months in most cases.

In order to discuss quantitative aspects of hemoglobin gain or loss, it is essential to know the blood volume. This datum is practically nonexistent for premature infants. Therefore, we determined the blood volume with Evans blue dye (T 1824) in 40 premature infants ranging in age from 1 to 94 days and in weight from 1,250 to 3,800 gm. The results indicated that the average premature infant begins life with a blood volume of about 110 cc. per kilogram of body weight and that this falls to about 75 cc. at 6 to 7 weeks of life, at which point it seems to remain. Serial studies in six infants in different weight groups indicated that this trend holds true for all.

With knowledge of the blood volume, hemoglobin concentration, and fetal and adult hemoglobin percentages, it becomes possible to speak in terms of total body hemoglobin and its component parts of total body fetal and adult hemoglobins. It is also possible to describe changes in hemoglobin mass apart from those factors which affect hemoglobin concentration, such as rate of growth, hemodilution, etc. The data obtained in these investigations seem to allow the following conclusions:

1. During the first 4 to 6 weeks of life in the prematurely born infant, there occurs virtual cessation of both fetal and adult hemoglobin synthesis. The duration of this period is inversely proportionate to the maturity of the infant.

2. The initial red blood-cell population present in the premature infant has a decreased survival time, so that an element of increased rate of red blood-cell destruction is also a factor.

3. The decreased hemoglobin synthesis plus the hemolytic element leads to a marked loss in total hemoglobin in the first 4 to 6 weeks.

4. At 4 to 6 weeks there occurs a sharp sustained production of adult hemoglobin synthesis and, interestingly enough, a definite, though temporary, resumption of fetal hemoglobin synthesis. The establishment of adult hemoglobin synthesis leads to a gain in total body hemoglobin, so that the hemoglobin concentration levels off despite continued weight gain.

5. It requires 14 to 16 weeks for the infant to regain the hemoglobin mass with which he was born. Thus, for this period of time more iron is available than is being utilized for hemoglobin synthesis, and added iron is not indicated. After this period, failure to supply additional iron leads to decrease in the rate of hemoglobin formation.

6. Preliminary evidence indicates that the administration of transfusions may retard the spontaneous resumption of hemoglobin formation.

DISCUSSION

Dr. Clement A. Smith, Boston: I am very much interested in the blood volumes of the premature infants, which are the kind of data we have long awaited.

We must remember that fetal hemoglobin is not of itself, as people have a way of believing, an inferior sort of pigment, or even perhaps a superior pigment. Thus, I don't believe it has ever been shown that it has anything to do with a lack of resistance or hemolysis of red cells. It seems to be a characteristic of other proteins of the fetus that they are different from the adult form. Apparently there are differences between fetal and adult myoglobin.

I think fetal hemoglobin is a sort of label, identifying it as made by a fetus, or a baby that has recently been a fetus. It is interesting that the babies' tendency to make a little fetal hemoglobin showed very nicely in Dr. Schulman's material to parallel his tendency to make much more adult hemoglobin. I don't want to start an argument, but should like to know whether Dr. Schulman gives his premature infants any iron before they are 6 or 8 weeks of age.

Dr. Wolf W. Zuelzer, Detroit: I want to thank Dr. Schulman for this beautiful piece of work. The subject discussed has bothered everybody for a long time. At one time we had hoped to do it, to measure blood volumes of premature infants, but we found the technical difficulty too great for us, and I think it is a magnificent achievement to have done that.

I wonder if Dr. Schulman, in his discussion, would clarify his thinking as to the physiologic implications of his findings and whether he has any correlation with reticulocyte counts and bone-marrow activity. For some years it has been our feeling, on the basis of pathologic observations, that the anemia of prematurity is really "physiologic" for the premature infant, if one can speak of anything physiologic in such an animal. In the presence of hemolytic processes, one finds a very marked reticulocytosis, in contrast to the older theory of marrow depression in the premature infant.

I wonder whether Dr. Schulman has data to clarify that particular problem. The kind of data he has presented will perhaps give us the answer to the question as to whether we are justified and whether it is wise or unwise to use transfusions on premature infants routinely, and if so, at what level one should transfuse.

Dr. Katharine Dodd, Little Rock, Ark.: I should like to ask a practical question of Dr. Schulman. Suppose your patients, instead of being nicely followed by public health nurses, disappear at the age of about 6 weeks up the creeks and into the swamps? Does it do any good to give iron intravenously to such patients, or is it useless unless you can catch them at this period? When we have premature infants, they are all right until we send them home. When we see them again many months later they have low hemoglobin values because no physician has seen them or given them any iron.

Dr. James A. Wolff, New York: I should like to congratulate Dr. Schulman for his excellent study, and particularly for his use of blood volumes in order to determine the total hemoglobin mass in the anemia of prematurity. As far as I know, this is the first time that blood-volume studies have been made. I should like to ask a question.

From Dr. Schulman's data, it would appear that the use of iron in the early days of the anemia of prematurity would not be indicated and that iron should be reserved for the period after 3 months of age.

This has been a controversial question in the past, and there have been numerous opinions expressed.

We have recently studied the effect of iron on the anemia of prematurity in the first three months when iron was given within a few days of birth. It would appear from that study that iron is effective in ameliorating but not preventing the drop in the red-blood-cell and hemoglobin levels that are expected in the untreated infant.

This is somewhat at variance with Dr. Schulman's findings, and I wonder whether or not it might be explained by postulating that medicinal iron is used preferentially to tissue iron in the body—in other words, that it may form a labile pool of iron for bone-marrow use.

I should also like to say that the use of transfusions, in our experience, has been the subject of investigation, and it would appear from our findings that transfusions are rarely needed for the premature infant, even the very small ones, unless there is a concomitant infection or some other clinical indication.

DR. ARTHUR F. ABT, Durham, N. C.: With reference to the last discusser, it seems to me that the iron preparations must be better than in the late 1930's, because I never had any iron which could prevent the anemias of premature infants.

I was always impressed with the early polycythemia and the drop in the red blood cells. It seems to me that you must consider the decreased number of cells as well as just the hemoglobin.

DR. CHERNOFF, St. Louis: I should like to ask Dr. Schulman if he has had an opportunity to study any infants who have continued to produce very high quantities of fetal hemoglobin into the first and second years of life and whether the patterns are similar to those of the premature infants.

DR. PETTER KARLBERG, Stockholm, Sweden: Together with Dr. Mildred Stahlman, I have followed the total hemoglobin in about 30 full-term newborn babies during the first six to eight weeks of life. We have used a CO method, in which the CO concentration in the blood is calculated from the determined CO concentration in the alveolar air after equilibrium is established in a closed respiratory system.

The total hemoglobin—the sum of the fetal and adult hemoglobin—in the normal newborn infant we have found to be about constant from the first week of life to the fifth or seventh week, after which time it starts to increase.

From the total hemoglobin and the hemoglobin concentration we have calculated the blood volume. The blood volume starts to increase at approximately the second week roughly parallel with the baby's increasing body weight. This should, at least partly, explain the so-called physiological anemia of the newborn infant as a dilution of the blood.

In some of the cases, we have also determined the plasma volume with the Evans-blue method. From the plasma volume and from the red-blood-cell volumes obtained from the total hemoglobin values, we have calculated the ratio between the mean body hematocrit value and the venous hematocrit value. The average value for this ratio was 0.82, which is about the same as Mollison obtained. In our studies this figure, however, tended to be somewhat lower in bloods with greater hemoglobin concentrations.

I should like to ask if in the investigation presented the blood volumes are corrected for the difference between the mean body hematocrit value and the venous hematocrit value and if, in that case, a constant value has been used? If the ratio does change, as our results suggest, the use of a constant factor would cause blood volumes calculated from plasma volumes to be falsely high during the first few days of life as compared with those later when hemoglobin concentrations are lower.

In addition to what I have said about the total hemoglobin during the first weeks of life, I should like to add that we have also started in Stockholm to study babies with high birth weight. In these babies, the total hemoglobin, instead of remaining constant, seems to decrease slightly during the first five or six weeks of life and then starts to increase. So we have found a negative relation between the slope of the total-hemoglobin curve (expressed as the angle-coefficient of the regression line) during the first five to six weeks of life on the one hand and the birth weight on the other.

DR. IRVING SCHULMAN, New York: I am delighted with all the discussion, and I should like to thank everyone.

First, in answer to Dr. Clement Smith, we certainly do not think that the fetal hemoglobin is the reason that the cells are destroyed more readily. As a matter of fact, we have submitted for publication a paper which denies the hypothesis that fetal hemoglobin, per se, is a determinant of erythrocyte longevity. We believe that the factor of cell size may be involved and, possibly, other factors which contribute to the ill-defined designation of immaturity.

About the administration of iron, I believe that Dr. Smith asked what we did about this and what we do about it now. When we ran this study, of course, we did not give any iron to any of these babies until we came to the points we have indicated here. I think now—and we have to have discussion with the chief of the department about this—we are probably going to arrange some sort of more-or-less mean system whereby we can protect all the infants and yet not give excess iron, because in our laboratory we are worried about the problem of iron overload, as well as iron deficiency.

Dr. Zuelzer asked some questions about the physiology of these changes and why they happen. I do not know why they happen. There are certain things, however, that we do know. As part of a controlled oxygen study, we do know that the differences between the oxygen concentrations in the incubators and in the atmosphere do not make any difference hematologically. If oxygen is involved at all, it would seem that the difference between the oxygen concentration in utero and in the atmosphere is sufficient without any added influence from the oxygen concentrations employed in nursery incubators.

We have done reticulocyte counts and have found that they are high at birth and drop practically to zero in the first week. A reticulocytosis appears again at five or six weeks, when the adult hemoglobin synthesis begins.

Concerning the physiological need for transfusion, as Dr. Zuelzer implied, in this entire group we gave a transfusion to only one baby, and in retrospect we were sorry about that, because when we calculated the data for this baby we found evidence that he was on the way to recovery before we gave the transfusion.

We do not at the present time have any lower limit or any limit at all at which we give transfusions to infants, and we try to give transfusions to them for clinical symptomatology.

About intravenous iron, there seems to be no question, from the available evidence, that if one gives it, it will be stored and used when necessary. All the evidence indicates that any iron in storage in the body is available for hemoglobin synthesis. The question occurs as to what this extra iron would do to the livers of these babies, where it is stored; there is much work to do concerning the effect of iron overload on liver structure. With these babies disappearing into the woods, possibly it would be a good idea to give them intravenous iron which would be stored, not excreted, and would be utilized at a later date.

Dr. Wolf's question about iron therapy and what it seems to do to the hemoglobin levels, we have discussed before and we will discuss many times again, I know. All I can say is that owing to limitations of time, I did not give other data which bring in other factors, such as the rate of growth and so on, and I think that any clinical investigation basing the judgment of results on the hemoglobin concentration alone requires an extremely well-controlled study of various factors, the predominant ones being the initial birth weight and the rate of growth.

Dr. Abt asked about the red blood cell count which, of course, we did, and I can say this: For the first three months, the red blood cell count and the hemoglobin concentration fall together. After this point, without additional iron, an iron-deficiency state may supervene, the hemoglobin levels fail to keep pace with the red blood cell counts, and hypochromia appears.

We have used Dr. Chernoff's method here, and I am delighted to see him.

We have attempted to find evidence of persistence of fetal hemoglobin, and the most obvious place we looked was in children born with cyanotic congenital heart disease. One might expect that these children would continue to make fetal hemoglobin. In these studies, however, no abnormal amounts of fetal hemoglobin were encountered.

Similar results have been reported by Adams.

Dr. Karlberg's questions were, of course, very important and involve the basic techniques for performing and for calculating blood volumes. The figure 0.83, to which he referred, is derived by multiplying the factor for trapped plasma in the hematocrit reading (0.95) by the factor expressing the relationship of the whole-body hematocrit reading to the venous hematocrit reading (0.87). We were aware of Mollison's work and went over it very carefully and also all other reported work in infants and children. In going over Mollison's data for newborn infants, we found that the factors seemed to remain constant even for very small babies. We decided, therefore, to use the factor 0.83 to calculate our data. If further work proves this assumption wrong, the magnitude of changes so produced will probably be minimal in any case.

The influence of dilution as pointed out by Dr. Karlberg led us to express the blood-volume data in terms of cubic centimeters per kilogram of body weight. In an individual child the progressive increases in total blood volume, as a function of body weight, contribute, of course, a dilution effect and to the development of anemia which may be more or less severe dependent upon the rate of growth. It was for this reason that we decided to try to get away from hemoglobin concentrations and to express our data in terms of total body hemoglobin and its component parts.

I thank everyone again, and I hope I have answered most of the questions.

(To Be Continued)

Abstracts from Current Literature

Biochemistry; Bacteriology and Pathology

Effect of Antireticular Cytotoxin on Cellular Defense (Phagocytosis). E. Lanzoni, Clin. pediat. **34**:543 (Aug.) 1952.

Antireticular cytotoxic serum is produced in animals which have received injections of spleen and bone marrow tissue of other animals and of men. When this serum is injected into humans, in small doses, it will act as a stimulant of the reticular endothelial system, and in large doses, as a depressant. In the present study, the phagocytic index in the leucocytes of the blood of 10 children was determined before, during, and after a course of injections of antireticular cytotoxic serum had been given; an increase in the phagocytic action of the leucocytes for staphylococci followed the injections.

Higgins, Boston.

Metabolism; Infant Feeding; Milk and Other Foods

Further Studies of the Use of Meat in the Diet of Infants and Young Children. Ruth M. Leverton, George Clark and Paul M. Bancroft, J. Pediat. **40**:761 (June) 1952.

The authors report that meat may be given to infants as young as 6 weeks without interfering with milk consumption. Infants who received meat showed increased hemoglobin and red cell values. Finally, meat-fed infants had fewer colds.

Macdonald, Pittsburgh.

Influence of Potassium on Tissue Protein Synthesis. Paul R. Cannon, Laurence E. Frazier, and Randolph H. Hughes, Metabolism **1**:49 (Jan.) 1952.

The authors report a series of experiments on rats first subjected to a period of protein depletion. When placed on an adequate repletion diet subsequently, the animals quickly recovered lost weight. The influence of the potassium content of the repletion diet on the weight curves of the animals was studied and the following conclusions were drawn:

Despite adequacy of the repletion diet, weight recovery was considerably retarded when the diet was free from potassium. This retardation was partially due to poorer caloric intake of the animals which were given no potassium, but it persisted even when the margin of difference in caloric intakes was narrowed between the groups receiving and not receiving potassium. The upper limit of requirement of potassium was 20 to 25 mg. per day (or 100 to 125 mg. per kilogram) and quantities greater than this did not accelerate weight recovery. Feeding of Aminosol and Amigen, both of which are protein hydrolysates, "excellent" so far as their amino-acid contents are concerned, was not followed by adequate protein repletion unless potassium salts were added to the basal ration.

Kaplan, Cincinnati.

Metabolism of Radioactive Cholesterol in the Intact Rat. D. Kritchevsky, Martha R. Kirk, and Max W. Biggs, Metabolism **1**:254 (May) 1952.

Radioactive cholesterol (labeled with C^{14} and H^{3}) was fed to rats. The data indicated that all, or part, of the cholesterol molecule was utilized in the formation of fatty acids, glycogen, phospholipid, and, presumably, other steroids.

Kaplan, Cincinnati.

GALACTOSEMIA: REPORT OF CASE WITH AUTOPSY. ALBERT M. EDMONDS, GORDON R. HENNIGAR, and ROBERT CROOKS, Pediatrics **10**:40 (July) 1952.

A case of proved galactosemia in a 2-month-old girl with necropsy findings has been reported. The liver lesion in the case reported does not clearly fit into the category of Laennec's cirrhosis or biliary cirrhosis. The presence of the adenomata, rich in glycogen, and the peculiar acinar structures separate it into a distinctive type of lesion. It is proposed that these cases represent congenital and familial cirrhosis.

The administration of large amounts of galactose to rabbits failed to produce liver cell degeneratation or necrosis.

As suggested from the cases reported in the literature and in view of the lack of agreement on the pathogenesis among observers, the same mechanism may not be responsible for all of the cases of galactose diabetes recorded.

FROM THE AUTHORS' SUMMARY.

NUTRITIONAL RECOVERY SYNDROME: PRELIMINARY REPORT. FEDERICO GÓMEZ, RAFAEL RAMOS GALVÁN, and JOAQUÍN CRAVIOTO MUÑOZ, Pediatrics **10**:513 (Nov.) 1952.

This paper presents clinical and laboratory data which indicate the development of a syndrome heretofore undescribed and still incompletely studied which appears in children during recovery from severe malnutrition.

The principal clinical findings are portal-intrahepatic hypertension beginning 20 to 40 days after treatment is instituted and lasting about a month.

Hepatomegaly, which is the first sign, is marked and progressive, affects particularly the left lobe, and is inversely proportional to the degree of fatty infiltration of the liver, as is demonstrated by liver biopsies.

Along with the hepatomegaly there is distention of the abdomen, a thoracoabdominal venous network, and ascites.

Later phenomena (occurring after about 60 days of treatment) are hypertrichosis of the forehead, back, and thighs, and a more or less marked eosinophilia not explained by intestinal parasites or allergy.

The most important chemical finding is the hypergammaglobulinemia, the highest level of which coincides with the appearance of the portal hypertension; this is definitely statistically significant. At the same time, a considerable elevation of total plasma proteins takes place and thymol turbidity tests become progressively more abnormal.

FROM THE AUTHORS' SUMMARY.

PATTERN OF GROWTH OF SELECTED GROUPS OF BREAST-FED INFANTS IN IOWA CITY. SILVIO L. PAIVA, Pediatrics **11**:38 (Jan.) 1953.

The data of measurements of 21 male and 24 female breast-fed infants from birth to 6 to 7 months of age are presented. The infants were born of well-fed mothers, coming from families of better than average income and intelligence. The pattern of growth of these infants is compared with that of a larger group, the majority of whom are artificially fed infants of the same socioeconomic status. It is concluded that the pattern of growth of the breast-fed infants does not differ significantly from that of artificially fed infants of the same socioeconomic group.

FROM THE AUTHOR'S SUMMARY.

EFFECT OF HIGH FAT DIET ON THE POTASSIUM DEFICIENCY SYNDROME IN THE RAT. H. S. PERUE and P. H. PHILLIPS, Proc. Soc. Exper. Biol. & Med. **81**:405 (Nov.) 1952.

A diet containing 0.03% potassium and 20% corn oil produced a greater incidence and extent of myocardial necrosis with fibrosis and dilatation of renal tubules typical of potassium deficiency than did an isocaloric 5% corn oil diet containing the same amount of potassium. No statistically significant differences were observed in other criteria of potassium deficiency.

HANSEN, Galveston, Texas.

COMPARATIVE BIOLOGICAL VALUES OF VARIOUS SUGARS USED IN INFANT FEEDING. MADELEINE VANSTEENBERGHE, Presse méd. **59**:1239 (Sept. 22) 1951.

The majority of pediatricians find that a combination of monosaccharides and polysaccharides is best tolerated by infants. The author shows that rats fed solely on a mixture of dextrin and maltose produced by hydrolysis of starch or a malt flour will survive longer than rats fed on refined sugars only. The difference may lie in the greater mineral and protein content of the mixture.

DAFFINEE, Melrose, Mass.

SUGAR METABOLISM IN ATROPHIC INFANTS. L. BARTA and F. V. LUKACS, Ann. paediat. **179**:91 (Aug.) 1952.

After injecting a 7.5% dextrose solution intravenously into atrophic infants, giving 0.75 to 1.5 gm./kilogram of body weight, a particularly good sugar tolerance was observed together with a Staub effect. The flat sugar curve and the deficient Staub effect after oral administration are ascribed to poor sugar absorption. The practical value of intravenous dextrose administration is pointed out.

FROM THE AUTHORS' SUMMARY.

CLINICAL RESULTS FROM THE THERAPEUTIC USE OF CAROB FLOUR IN THE CHILD'S DIET. M. MALASPINA, Minerva pediat. **4**:264 (April 15) 1952.

Four years' experience with 470 children and infants with nutritional and gastrointestinal diseases has indicated that the carob flour preparations were well tolerated by the undernourished infant and also by infants with celiac disease, gastroenteritis, and typhoid.

HIGGINS, Boston.

Vitamins; Avitaminoses

COMPARATIVE TOXICITY OF AQUEOUS AND OILY PREPARATIONS OF VITAMIN A. J. M. LEWIS and SIDNEY Q. COHLEN, Pediatrics **9**:589 (May) 1952.

Vitamin A toxicity in the rat as manifested by mortality rate and incidence of spontaneous fractures was greater after the administration of excessive amounts of vitamin A in an aqueous menstruum than after a similar intake of the vitamin in an oily vehicle. Liver damage due to vitamin-A toxicity impaired the ability of the liver to store the vitamin. Ingestion of toxic doses of the aqueous preparation resulted in greater depression of liver storage than comparable amounts of the oily product. The mechanism of vitamin A toxicity is discussed.

FROM THE AUTHORS' SUMMARY.

VITAMIN A DEFICIENCY: CASE REPORT; UNUSUAL MANIFESTATIONS IN A 5½-MONTH-OLD BABY. DAVID CORNFIELD and ROBERT E. COOKE, Pediatrics **10**:33 (July) 1952.

A case of vitamin-A deficiency in a 5½-month-old infant is presented. The multiple manifestations of vitamin-A deficiency as noted in this case clearly resemble the signs of deficiency described in experimental animals. The need for adequate supplementation of synthetic diets is reemphasized.

FROM THE AUTHORS' SUMMARY.

Hygiene; Growth and Nutrition; Public Health

THE NORMAL INFANT: HIS DEVELOPMENT AND BEHAVIOR. E. B. SIMS, Clin. Rep. Adelaide Child. Hosp. **2**:81 (Nov.) 1951.

The author discusses briefly the current trends in management of the young child from the developmental aspect.

MCGUIGAN, Evanston, Ill.

Prematurity and Congenital Deformities

THE INFLUENCE OF MATERNAL AND OBSTETRICAL FACTORS ON FETAL SURVIVAL. JAMES L. FITZGERALD JR., GEORGE N. FERRIS, and CLARENCE E. TOSHACH, Am. J. Med. Sc. **222**:40 (July) 1951.

This study concerns 52 premature and 82 mature infants that failed to survive in a series of 3,751 deliveries. Of this group, congenital anomalies incompatible with life were the designated cause of death in 24.6%. The corrected fetal mortality, excluding malformations, is 1.8% of all mature infants. For the premature infants of all 3 groups, the corrected mortality is 15.3%.

Of premature infants, 43% have obstetrical or maternal complications which definitely influence adversely their chance to survive. Of mature infants, these factors were present in 74.5%. The autopsies were performed on 64% of the infants in this series. The authors conclude that breech delivery presents the greatest hazard to both mature and premature infants.

Better psychological preparation for the onset of labor, as practiced in various clinics, will decrease the need for sedation. A normal infant is the goal, not an amnesic and well-anesthetized mother. Irrespective of the birth weight of premature infants, a child born without the handicap of obstetrical complications or a sick mother has an excellent chance to survive.

HENSKE, Omaha, Neb.

FEEDING PREMATURE INFANTS: RECENT MODIFICATIONS IN THE IN-DWELLING NASOGASTRIC TUBE METHOD. STEPHEN ROYCE, California Med. **77**:301 (Nov.) 1952.

In a two-year period some 600 premature infants were fed through an in-dwelling plastic nasogastric catheter. The results suggest that this method is practical and less fatiguing than gavage or dropper feeding. To increase the ease and safety of this procedure, certain modifications in the technique of taping the catheter and of preparing its leading end are suggested.

PRYOR, Redwood City, Calif.

SALMONELLA INFECTION IN A PREMATURE INFANT WITH CONGENITAL ANOMALIES. JOHN EMMET and JOHN M. CHAPMAN, California Med. **77**:340 (Nov.) 1952.

A case of Salmonella typhimurium infection causing severe diarrhea in a premature infant with complete atresia of the duodenum, surgically corrected, is presented. Epidemiological evidence indicated that the mother was the source of the infection and placed the minimum incubation period at 11 days, the maximum incubation at 16 days.

PRYOR, Redwood City, Calif.

ANEMIA OF THE PREMATURE INFANT: A TWO-YEAR STUDY OF THE RESPONSE TO IRON MEDICATION. M. E. REEDY, S. O. SCHWARTZ, and E. B. PLATTNER, J. Pediat. **41**:25 (July) 1952.

The smaller the premature infant the more he needs iron. The authors started supplemental administration of iron to the newborn on the seventh day of life. They used a commercial mixture of liver concentrate, copper sulfate, and iron and ammonium sulfate.

The premature infants that received iron gained weight faster and obtained higher hemoglobin values than the controls.

MACDONALD, Pittsburgh.

PARAFFIN-TIPPED POLYETHYLENE TUBING FOR FEEDING OF PREMATURE BABIES, INFANTS, and CHILDREN. HANS W. KUNZ, J. Pediat. **41**:84 (July) 1952.

It has become popular to feed some premature infants through an in-dwelling polyethylene tube. In spite of preliminary smoothing of the ends of these tubes, their introduction may traumatize the nasopharynx and they may injure, even perforate, the gastric mucosa. A coating of paraffin over the smoothed end of the polyethylene tube will minimize this trauma.

MACDONALD, Pittsburgh.

PREMATURE INFANTS IN LATER LIFE: STUDY OF INTELLIGENCE AND PERSONALITY OF TWENTY-TWO PREMATURE INFANTS AT AGES EIGHT TO TWELVE YEARS. PHILIP J. HOWARD and CALIER H. WORRELL, Pediatrics **9**:577 (May) 1952.

In this study a few physical defects were found, consisting of malnourishment, dwarfism, obesity, hypothyroidism, congenital absence of tooth buds, scoliosis, and cryptorchidism. One child showed keratitis at birth. Eleven children were hyperopic. The condition of the eyes leads to the conclusion that the eyes of premature infants may be frequently defective. Otherwise it is difficult to say that prematurity itself affects the physical growth.

The intelligence quotients of the 22 children studied ranged from two of the high grade moron group, upward, with a fair distribution, to two in the very superior intelligence group. Prematurity per se seemingly has neither a beneficial nor a detrimental effect on intelligence except that a more than average percentage of premature infants suffer intracranial hemorrhage as a result of being born prematurely. In these studies, one child was given a definite diagnosis of brain damage at birth, and others were suspected of this damage. This seemingly appears in the intelligence quotient with a higher than expected incidence of mild mental retardation. When birth weight was used as a criterion, there was no relation between the degree of prematurity and the resultant intelligence quotient.

Personality test results, in addition to the information gleaned from the psychologic interviews and the histories, show that over half have made unsatisfactory or below-average personality adjustment. Contributing factors were found including prematurity, overprotection by the parents, and poor physical endowment. Twelve of the 22 had personalities of the submissive-passive type. Eight of the 22 showed unusual aggressive tendencies. Other behavior aberrations uncovered were nail biting, two cases of habit spasms, and one case of chronic masturbation. It is suggested that study of premature infants who are necessarily deprived of immediate postnatal maternal tenderness may finally offer a basis for assessing the theory that such tenderness is necessary.

RETROLENTAL FIBROPLASIA: ANIMAL STUDIES. W. R. HEPNER JR., Pediatrics **9**:602 (May) 1952.

This is a study of induced vascular engorgement and hyperplasia of the iris, tunica vasculosa lentis, and retina in kittens. A condition similar to the early retinal stages of retrolental fibroplasia, along with persistence of the ocular embryonic vascular system, is induced by repeated massive blood transfusions to chronically edematous kittens.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL ABSENCE OF THE SPLEEN: SYNDROME WITH ATRIOVENTRICULARIS AND SITUS INVERSUS. DONALD W. POLHEMUS and WILLIAM B. SCHAFER, Pediatrics **9**:696 (June) 1952.

Four cases of congenital absence of the spleen are presented with a review of the literature. It is noted that this anomaly usually occurs as a syndrome with persistent atrioventricularis communis, partial situs inversus of the abdominal viscera, and accessory lobes of the lung.

FROM THE AUTHORS' SUMMARY.

EXPERIMENTAL USE OF METHYL TESTOSTERONE AND TESTOSTERONE IN PREMATURE INFANTS. HORST A. AGERTY and JOSEPH N. SEITCHIK, Pediatrics **10**:28 (July) 1952.

One hundred premature infants weighing between 1.8 and 2.3 kg. were studied in respect to time to regain birth weight, time to gain to 2.5 kg., rate of weight gain, and protein-nitrogen intake. Fifty-five received an androgen either orally or parenterally. The infants received a diet of varying protein content. While the results suggested a minimal protein- anabolic effect

in all the treated infants, this was associated with a decreased nitrogen intake. Thus no clinical benefit resulted. Neither the method of administration of the androgen nor the protein content of the diet offered influenced the results.

FROM THE AUTHORS' SUMMARY.

LEVEL OF HYALURONIDASE INHIBITOR IN THE SERUM OF PREMATURE INFANTS WITH RETROLENTAL FIBROPLASIA. JULIA B. MACKENZIE, Pediatrics **10**:533 (Nov.) 1952.

The serum of the premature infant contains material which inhibits bovine hyaluronidase. This inhibitor was found to be present to about the same degree in infants with and without retrolental fibroplasia and appeared to be unrelated to the severity of the disease.

The level of the physiologic inhibitor of hyaluronidase found in the blood of the premature and full-term infant is approximately of the same order of magnitude.

FROM THE AUTHOR'S SUMMARY.

ANOMALIES OCCURRING IN CHILDREN EXPOSED IN UTERO TO ATOMIC BOMB IN HIROSHIMA. GEORGE PLUMMER, Pediatrics **10**:687 (Dec.) 1952.

A study was carried out on 205 children 4½ years old who had been exposed to the atomic bomb blast during the first half of the intrauterine life. Eleven were exposed within 1,200 meters of the bomb hypocenter, and the remaining 194 were beyond this distance.

Seven of these 11 children exposed within 1,200 meters had microcephaly with mental retardation. This diagnosis was not made for any of the 194 children exposed at greater distance.

Correlation between head size and mental development of the child with distance from the hypocenter, symptoms of radiation effect, and type of shielding of the mother are discussed.

The conclusion drawn from the present study is that central nervous system defect can be produced in the fetus by atomic bomb radiation, provided that exposure occurs within approximately 1,200 meters of the hypocenter and that no effective shielding, such as concrete, protects the fetus from direct irradiation.

It is impossible to publish accurate radiation dosage data for the exposed mothers because this is restricted material. Obviously the dosage range must have been high to produce epilation and purpuric phenomena (COMMITTEE ON ATOMIC BOMB CASUALTIES, NATIONAL ACADEMY OF SCIENCES).

FROM THE AUTHOR'S SUMMARY.

RETROLENTAL FIBROPLASIA. M. LELONG, G. RENARD, A. ROSSIER, C. LEMASSON, and J. MICHELIN, Presse méd. **59**:705 (May 23) 1951.

The eyegrounds of each premature infant at the *École de Puériculture* in Paris have been systematically examined during the past few years. In that time, 146 premature infants weighing less than 1,800 gm. have been followed by the authors. Of this number, 11, or 6.8%, displayed evidence of retrolental fibroplasia.

The authors stress the need for early diagnosis, with the possibility of reversal of the process by some specific treatment. They consider the condition to result from some postnatal factor or factors on the immature retina. They suggest the possibility of overadministration of oxygen.

DAFFINEE, Melrose, Mass.

THE ORIGIN OF CONGENITAL MALFORMATIONS. PAUL GIRAUD, Presse méd. **60**:1125 (Aug. 16) 1952.

The incidence of congenital malformations has notably increased in recent years, and it raises a problem to which the suggested solutions may be applied only in very few cases. Embryopathy, deficiencies during pregnancy, and Mendelian heredity, even of recessive type, afford an adequate explanation in the approximate proportion of 2 cases out of 10. Usually both procreators seem

normal and free of transmissable defects, whereas the offspring shows debility or malformation. It is probable that germinal degeneration in apparently healthy persons would arise from infectious or toxic causes or also from mistakes in hygiene, and would be a significant factor in reduction of the vital potentiality of the fetus. Such causes are the more detrimental when they originate in periods close to puberty. Perhaps it is necessary to reconsider all our rules regarding education and care of children and adolescents with a view to this "social function of reproduction."

FROM THE AUTHOR'S SUMMARY.

MORTALITY OF PREMATURE INFANTS AT THE CLINIC IN BASEL 1939-1949. J. COHEN, Ann. paediat. **179**:109 (Aug.) 1952.

In a study of 1,252 premature babies treated in the Basler Kinderspital during 1939-1949 the author found a great rise in the number of premature babies admitted to this hospital during the last 10 years. The average birth weight of the admitted premature babies shows a tendency to fall. The total mortality is rising on account of the rising early mortality, and the late mortality is declining. This decline is most likely caused by the introduction of sulfonamides and the antibiotics. The decrease of the average birth weight and the introduction of the new drugs have an antagonistic effect, which makes the appraisal of each factor by itself difficult. The causes for the late mortality are given according to their importance: enteritis, interstitial virus pneumonia, aspiration pneumonia, other infections, and bronchopneumonia.

FROM THE AUTHOR'S SUMMARY.

INFLAMMATIONS IN THE EMBRYO AND FETUS IN EXPERIMENTAL VIRUS INFECTIONS IN ANIMALS. VON S. SCHEIDEGGER, Bull. Akad. med. Wissensch. **8**:346 (July) 1952.

An experimental investigation of the histopathological changes in the embryo or fetus in certain virus disease of the animal was undertaken. Into pregnant white mice and in guinea pigs, and partly also into incubating hen's egg, certain virus infections were introduced, and after a fixed interval of time the embryo or fetus was examined. The experiments were made with certain strains of ectromelia, psittacosis, and rabies. Especially severe changes of a degenerative and inflammatory type were found in the liver, myocardium, spleen, and lymph node. The sensory epithelium was also partly changed. The reactions were not the same as those seen in the mother animal. In the case of rabies, the chick embryo showed no significant changes.

FROM THE AUTHOR'S SUMMARY.

EXPERIMENTAL STUDY OF THERMIC TREATMENT FOR THE IMMATURE INFANT. M. BERNARDI, Minerva pediat. **4**:495 (June 30) 1952.

The author describes an incubator he has devised for the maintenance of a stable body temperature and heat balance in the immature infant. He also describes thermocouples for determining the cutaneous, subcutaneous, and rectal temperatures of these infants. He expresses the opinion that the immature infant has a physiologically lower body temperature than the full-term infant. He favors the use of the incubator only for the exceedingly small baby and for patients with extreme heat lability.

HIGGINS, Boston.

Newborn

ERYTHROBLASTOSIS FETALIS IN THE NEGRO INFANT: REPORT OF FIVE CASES, INCLUDING FOUR CASES DUE TO A-B-O INCOMPATIBILITIES. ROLAND B. SCOTT, MELVIN E. JENKINS, and ALTHEA D. KESSLER, J. Pediat. **39**:680 (Dec.) 1951.

Most cases of erythroblastosis in Negro infants are due to A, B, and O blood group incompatibilities and not to Rh-sensitization, which is rare in this race.

MACDONALD, Pittsburgh.

URGENT SURGICAL CONDITIONS IN THE NEWBORN. ALVIN B. HAYLES, Minnesota Med. **36**:49 (Jan.) 1953.

Better surgical techniques augmented by better understanding of nutrition, fluid balance, and metabolism of electrolytes has led to great progress in surgical conditions of the newborn.

The problem of subdural hematoma is discussed. Congenital lesions of the respiratory system are reviewed. The author warns of the difficulty in management of the infant with a tracheotomy. The treatment of pneumothorax, congenital lung cysts, and anomalies of the great vessels is reviewed.

Congenital diaphragmatic hernia may result in both respiratory and gastrointestinal symptoms. Atresias and stenosis of the entire gastrointestinal tract are discussed.

STOESSER, Minneapolis.

SURGICAL APPROACH TO ATELECTASIS IN THE NEWBORN. W. S. WYATT, T. C. CHISHOLM, E. BERGLUND, and W. P. EDER, Minnesota Med. **36**:172 (Feb.) 1953.

Atelectasis of the newborn accounts for about 50% of all deaths in the neonatal period. The disease occurs most commonly in premature infants. The treatment in the past has been primarily symptomatic and quite unsatisfactory.

During the past thee years the authors have attempted a surgical procedure on 23 newborn infants who appeared to be succumbing to congenital atelectasis. The procedure consisted of making a small opening in the chest and applying positive air pressure up to 35 cm. of water applied through nose and mouth by a light fitting mask. Among the 23 babies operated on there were 11 survivals.

STOESSER, Minneapolis.

ERYTHROBLASTOSIS FETALIS: VIII. STUDIES OF SERUM BILIRUBIN IN RELATION TO KERNICTERUS. DAVID YI-YUNG HSIA, FRED H. ALLEN JR., SYDNEY S. GELLIS, and LOUIS K. DIAMOND, New England J. Med. **247**:668 (Oct. 30) 1952.

The authors reiterate the essential facts surrounding the most important complication of erythroblastosis fetalis, viz., kernicterus. The high mortality resulting from kernicterus and the permanent neurologic sequelae in those who survive make advance knowledge of the possibility of erythroblastosis mandatory so that treatment by exchange transfusion be considered and prepared for in advance. It has been proved that kernicterus is preventable by exchange transfusion, and it is known that kernicterus does not occur in the absence of considerable jaundice.

Bilirubin levels were compiled from normal babies, babies with erythroblastosis, and babies who had received exchange transfusions. It was clear that exchange transfusions materially lowered bilirubin levels and that kernicterus was likely to occur in babies with serum bilirubin levels above 30 mg. per 100 cc. and unlikely to occur when the serum bilirubin remained below 20 mg. per 100 cc. These data suggest that serum bilirubin determinations are a valuable aid as guides to the treatment of the erythroblastotic infant, with 20 mg. per 100 cc. regarded as the critical level. Multiple exchange transfusions may be necessary to keep the bilirubin below this figure. The authors discuss some of the yet unanswered questions concerning the production of brain damage in erythroblastosis fetalis with kernicterus.

WHEELOCK, Denver.

COAGULATION STUDIES IN THE NEWBORN INFANT: PART II. ERYTHROBLASTOSIS FETALIS. RUTH M. HEYN, IRVING H. ROZENFELD, BURTON J. GROSSMAN, and JAMES D. STUART, Pediatrics **9**:327 (March) 1952.

Determinations of the whole-blood clotting time, prothrombin concentration, protamine titration, platelet count, and gross observation of clot lysis were done on 10 infants with erythroblastosis fetalis on the first, third, and fifth days of life, and these results were compared with similar data obtained from normal babies.

On the first day of life, the erythroblastotic infants had a prolonged whole-blood clotting time and increased protamine titration as compared with normal babies, while the prothrombin concentration, platelet count, and clot lysis were comparable to those of normal infants.

FROM THE AUTHORS' SUMMARY.

TETANY AND PARATHYROID HYPERPLASIA IN THE NEWBORN INFANT: INFLUENCE OF DIETARY PHOSPHATE LOAD. L. I. GARDNER, Pediatrics **9**:534 (May) 1952.

Five cases of newborn tetany are described, and the relationship between dietary phosphate load and the manifestations of this disease are pointed out. An additional newborn infant was described who showed symptoms other than tetany in association with dietary phosphate load. Data concerning diet, cause of death, and degree of parathyroid hyperplasia are tabulated for eight newborn infants who were found to have parathyroid hyperplasia at autopsy. Similar data are tabulated for eight newborn infants and five older children who were found to have normal parathyroid glands at autopsy. Several other factors possibly involved in newborn tetany are discussed.

FROM THE AUTHOR'S SUMMARY.

TERATOMA OF THE NECK IN A NEWBORN INFANT: CASE REPORT. ROBERT R. WHITE and RUTH S. GOSSELIN, Pediatrics **9**:565 (May) 1952.

The case history of a 3-day-old infant with a huge teratoma of the neck, endangering the infant's life and necessitating immediate surgical attack, is presented. This report illustrates still another condition amenable to operative relief at an early age.

FROM THE AUTHORS' SUMMARY.

STUDIES OF THE IMMUNOLOGY OF THE NEWBORN INFANT. JOHN J. OSBORN, JOSEPH DANCIS, and JUAN F. JULIA, Pediatrics **9**:736 (June) 1952.

Forty infants from 1 week to 6 months of age who had no circulating antitoxin were immunized with one injection of a high-titer alum-precipitated diphtheria toxoid, and their antitoxin responses were followed at regular intervals up to six months afterward.

The ability to form antitoxin improved significantly during the first 2 months of life. No significant difference could be demonstrated between the response of infants 2 to 4 months old and that of infants 6 months old. (In the statistical tests, the 5% level was adopted as indicating significance.)

Twenty-seven of the above infants were immunized at the same time in the opposite arms with a single dose of alum-precipitated tetanus toxoid. The response to tetanus immunization was faster and better in infants from 2 to 6 months of age than in infants 1 month old and younger. The response to the tetanus toxoid preparation was faster and better than the response to the diphtheria toxoid preparation.

The following conclusions are drawn: (*a*) the infant can form antibodies from birth; (*b*) the ability to form antibodies improves during early life (for diphtheria and tetanus antitoxin, the improvement is rapid during the first two months and then is much slower), and (*c*) the advisability of early immunization is related to the potency of the antigen to be used.

FROM THE AUTHORS' SUMMARY.

PHAGOCYTIC AND AMEBOID ACTIVITIES OF THE LEUKOCYTES IN THE NEWBORN INFANT. YEHUDA MATOTH, Pediatrics **9**:748 (June) 1952.

Neonatal leucocytes obtained from cord blood were found to have lower ameboid and phagocytic activities than do maternal leucocytes and those of other adults.

FROM THE AUTHOR'S SUMMARY.

OXIMETER STUDIES IN NEWBORN INFANTS DURING CRYING. KLARA J. PREC and DONALD E. CASSELS, Pediatrics **9**:756 (June) 1952.

The arterial oxygen saturation was determined with a direct-reading single-scale oximeter on 135 healthy newborn infants during sleep and while crying. In the first group, consisting of infants from 1 hour 30 minutes to 3 days of age, 66% showed a decrease of oxygen saturation with crying, 27% an increase, and 6.8% no change. In the second group, which includes all infants between 4 and 9 days of age, 59% showed an increase in saturation with crying, 21% a decrease, and 22.4% no change. In comparison, the mean results for these two groups are in the opposite direction. These changes are statistically significant. Twenty-eight infants were studied also while breathing oxygen (73% to 98.5%), and the results were compared with those for infants in room air; the trends were identical.

It is concluded that increases in arterial oxygen saturation with crying, which occur most frequently in older infants, are probably due to an increase in alveolar oxygen tension secondary to improved pulmonary ventilation during crying.

The paradoxic decrease in saturation during crying, which was found in a large percentage of infants of the younger group, is suggestive of the presence of a transitory venous-arterial shunt. This shunt could be either through atelectatic areas of the lung or through the foramen ovale, which is only functionally closed and can open whenever the pressure in the right auricle exceeds the left auricular pressure. There is some available evidence to support the latter possibility.

FROM THE AUTHORS' SUMMARY.

OBSTRUCTION OF DUODENUM IN THE NEWBORN INFANT DUE TO ANNULAR PANCREAS. DANIEL J. SHAPIRO, FRANK J. DZURIK, and EDWIN W. GERRISH, Pediatrics **9**:764 (June) 1952.

Four cases of duodenal obstruction in the neonatal period caused by an annular constricting pancreatic ring are reported. These cases and the five others previously reported by different authors have been reviewed. Criteria were not found in this group of cases by which a definite preoperative diagnosis could be made. The etiology, embryology, and treatment of this condition in infants are discussed.

FROM THE AUTHORS' SUMMARY.

CHRONIC ULCERATIVE COLITIS: CASE REPORT IN A NEWBORN INFANT. SAMUEL L. BERANBAUM and ROBERT J. WALDRON, Pediatrics **9**:773 (June) 1952.

A case of ulcerative colitis in the newborn infant is presented with roentgenographic and postmortem data. This is the earliest case on record with roentgenograhic studies of the colon, the latter being made at 24 days of age.

FROM THE AUTHORS' SUMMARY.

AVAILABILITY OF VITAMIN E IN THE NEWBORN INFANT. PAUL GYÖRGY, GILBERT COGAN, and CATHARINE S. ROSE, Proc. Soc. Exper. Biol. & Med. **81**:536 (Nov.) 1952.

Blood was collected in 0.9% sodium chloride-1% sodium citrate solution, the suspension was centrifuged, the supernatant fluid withdrawn, and cells made up to 2.5% suspension with a mixture of equal parts isotonic saline and phosphate buffer, pH 7.4. After incubation and centrifugation, the supernatant fluid was withdrawn and a 5% suspension of the cells in isotonic saline made. Cell suspension was added to the phosphate buffer and hydrogen peroxide, incubated and allowed to stand; the contents of the tubes were mixed, and the color of the supernatant fluid was measured by photometer. Distilled water was added to effect complete hemolysis. The hemolysis test was carried out on 88 infants on the first, second, and fifth days of life. In another group of 17 newborn infants, tocopherol was added to the suspension. The degree of hemolysis before treatment was found to be 3% $\pm$ 4.5%, and after the addition of tocopherol, 0.6 $\pm$ 0.4%. Addition of tocopherol by mouth to newborn infants also affected hemolysis. Mixed tocopherol given to mothers in the last two to four weeks of pregnancy did not change the hemolysis test in the newborn.

HANSEN, Galveston, Texas.

Acute Contagious Diseases

THE RECOVERY OF VIRUS FROM REGIONAL LYMPH NODES OF FATAL HUMAN CASES OF POLIOMYELITIS. HERBERT A. WENNER, and EDWARD F. RABE, Am. J. M. Sc. **222**:292 (Sept.) 1951.

After fatal illness caused by poliomyelitis virus, regional lymph nodes and pancreatic tissues were obtained at necropsy from nine patients. Poliomyelitis virus was detected in lymph nodes obtained from six persons. The positive tests were distributed as follows: right axillary lymph nodes, positive in two; left axillary lymph nodes, positive in three; right inguinal lymph nodes, positive in two, and left inguinal lymph nodes, positive in two. Poliomyelitis virus was found once in mesenteric lymph nodes. The pancreatic tissues obtained from these nine patients did not contain detectable amounts of poliomyelitis virus.

The published results on the presence of poliomyelitis virus in lymphatic tissue were reviewed, and the results of the present study are discussed in view of antecedent data. The assumption is made, in view of a widespread distribution of poliomyelitis virus in lymphatic tissue, that during the invasive period poliomyelitis virus extends from a position in the gastrointestinal tract into lymphatic channels, with outflow into the blood stream and interstitial tissue spaces. From these compartments virus is transported to lymph nodes, where it may be detected for a period after the stage of viremia.

HENSKE, Omaha, Neb.

VIRUS ENCEPHALITIS DURING A POLIOMYELITIS EPIDEMIC: A REPORT OF FIVE CASES. I. DRAVIN, J. H. COFFEY, and W. C. DINE, Ann. Int. Med. **34**:705 (March) 1951.

Five patients with virus encephalitis were admitted to the hospital within a six-week period during a moderately severe epidemic of poliomyelitis. In four of these the disease was identified as western equine encephalitis, and in one as St. Louis encephalitis, by complement fixation and neutralizing studies.

The clinical pictures of western equine and St. Louis encephalitis are indistinguishable. The definitive diagnosis depends upon the neutralization and complement fixation tests. The cases presented here illustrate the extreme variability in the severity of western equine encephalitis, from the mild infection seen in one case to the extremely severe, fulminating form, seen in two cases.

All the patients recovered with only symptomatic, nonspecific therapy, despite the extreme severity of the disease in two. The newer antibiotics, chlortetracycline (aureomycin) and chloramphenicol, were unavailable, but they should be tried in cases of virus encephalitis, since certain other virus diseases have responded to them.

During the period in which these cases occurred, 18 cases of poliomyeilitis were reported. Because of a similar seasonal incidence, as well as the occurrence of many of the same clinical features in the two diseases, it is probable that many cases of virus encephalitis have been erroneously diagnosed as poliomyelitis. A spastic type of paralysis favors the diagnosis of encephalitis, but in nonparalytic forms serologic studies may be necessary for differentiation.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.]

SERUM NEURITIS. I. FISCHER, Ann. Int. Med. **35**:922 (Oct.) 1951.

Serum sickness has been estimated to follow the injection of various sera in about 15% of all cases in which they are used. As a rule, serum sickness is a transient affection, which responds promptly to the proper treatment (chiefly with epinephrine) and which terminates in complete recovery. Occasionally, however, it is followed by so-called serum neuritis.

Fischer reviews certain important features of serum neuritis, as they are emphasized in the literature. In the majority of the reported cases the disorder followed the injection of tetanus

antitoxin. Involvement of the peripheral nerves is the most frequent manifestation. Neuritic symptoms as a rule occur when serum sickness is most intense, although they may appear almost immediately after the onset or when the attack has almost disappeared. The course of events is usually that of severe pain in the neck, shoulders, arms, or legs, followed within hours or days by flaccid paralysis, muscle tenderness, and muscle atrophy. Loss of weight is frequently extreme. The pain may disappear promptly or may last for days, or even months. It is characterized by extreme severity. About 20% of all patients, according to Thompson and Tombleson, are left with permanent residua in the affected extremity, but the majority recover completely with such measures as general nutritive and vitamin therapy, immobilization of the affected part, local application of heat, and, later, physical therapy with graduated exercises.

In most respects, the case Fischer reports here fits into the pattern of other recorded cases, except that the condition occurred in a patient with a strongly psychotic background. Serum sickness developed on the eighth day after a prophylactic injection of tetanus antitoxin and was, as usual, transient. Serum neuritis developed 48 hours later. All manifestations had completely disappeared when the patient was hospitalized except for the local neuritic complication. The serum neuritis affected the brachial plexus, as it oftenest does, and the history of the intractability of the pain, in spite of ample sedation and analgesic medication, was entirely typical.

The patient remained in the hospital for 14 days. The brachial neuritis showed some improvement under immobilization, general supportive and vitamin therapy, and the local application of heat. Her mental and emotional status, however, deteriorated. She was on admission, and continued to be, in a highly emotional state, with frequent outbursts of crying, complaints of personal problems, etc. She was removed to another institution, where she remained for eight months.

She was reexamined 10 months after the onset of the serum neuritis. At this time abduction of the right arm was possible, but the muscles of the right shoulder and upper arm showed marked atrophy, and there was considerable difference in the strength of the hand grip on the right and on the left side. The muscles of the neck were stiff and were weaker than on first examination. There had been moderate loss of weight. The patient seemed somewhat more stable emotionally as the result of the intensive psychiatric therapy she had received during the eight-month period of hospitalization.

Fischer points out that this patient's strongly psychotic background probably had nothing to do with the development of the serum neuritis, but the serum sickness and subsequent neuritis undoubtedly precipitated the psychotic episode, for which a long period of treatment was necessary. He calls particular attention to the possible medicolegal aspects of the condition.

ALPERS, Philadelphia [A. M. A. Arch. Neurol. & Psychiat.].

THE SMALL HOSPITAL'S ROLE IN POLIOMYELITIS. EDWARD B. SHAW and H. E. THELANDER, California Med. **77**:32 (July) 1952.

Medical skills should be developed by the staffs of smaller hospitals for the differential study of patients with symptoms resembling those of poliomyelitis in order to provide the rudiments of care for the occasional patient with mild poliomyelitis, to recognize the indications which point to the necessity of superior technical assistance, and to decide when it is appropriate to move patients to better-equipped centers.

The impetuous acquisition of mechanical aids for the treatment of special problems will be effective in small communities only to the extent that this equipment is kept serviceable and is operated by persons of sufficient skill. Epidemic situations in a small community can be met only by mobilization of facilities under adequate direction and by integration of care with that provided by larger treatment centers.

PRYOR, Redwood City, Calif.

Orthopedic Care in Anterior Poliomyelitis. LeRoy C. Abbott. J. Pediat. **39**:663 (Dec.) 1951.

In recent years, physicians, particularly pediatricians, who see patients with poliomyelitis early in the disease have become so enthusiastic about the benefits of heat and passive movements of the joints that they have discarded orthopedic methods of treatment which are of established value in the prevention of crippling deformities. Abbott discusses the prevention and treatment of myostatic contractures during the subacute and convalescent stages of poliomyelitis as well as the prevention of overfatigue of paralyzed muscles resulting from continuous stretching. He also outlines surgical procedures in the convalescent and in the chronic stages of the disease.

Macdonald, Pittsburgh.

Effect of Inherited Antibodies on the Active Immunization of Infants. Louis Greenberg, and Donald S. Fleming, J. Pediat. **39**:672 (Dec.) 1951.

At the ages of 3 and 4 months, infants were immunized against diphtheria, tetanus, and whooping cough. One year later, titrations for the antibodies concerned showed satisfactory blood levels for diphtheria and for tetanus. When a potent antigen is used, inherited antibodies do not lower but merely delay the development of diphtheria antitoxin. Pertussis protection is difficult to evaluate, but after a year 84% of the immunized children showed a response as judged by agglutination tests.

Macdonald, Pittsburgh.

Studies on Poliomyelitis in Ontario: Further Observations on the Spread of Poliomyelitis and Coxsackie Virus Infections in Small Communities. N. Silverthorne, Canad. M. A. J. **64**:309, 1951.

This paper is part of an exhaustive study and cannot be adequately abstracted.

McGuigan, Evanston, Ill.

Epidemiological Study of Measles as Influenced by Mass Immunization with Gamma Globulin. R. L. Coigny and P. Straus, Presse méd. **59**:634 (May 9) 1951.

The movement of displaced persons from camps in Central Europe to Australia was complicated by the appearance of cases of measles in sufficient number to constitute an epidemic. The administration of gamma globulin to contacts under the age of 3 years in doses designed to modify the course of measles served only to produce milder forms of measles in the children so protected, with outbreaks arising from these cases which exploded on shipboard. The problem was then attacked by injecting a protective dose of gamma globulin to each child of 6 years or less before he left the camp of origin. Measles still appeared during the journey.

On the assumption that the immunization must have worn off and that a second exposure was occurring during this unguarded period, a third method was set up.

All children under the age of 6 years were given a protective dose of gamma globulin 16 days before their expected date of departure from the camp of origin. Twenty-one days after this injection, and on every 21st day of their journey, another protective dose was administered.

Under this system, the measles situation was held completely in control.

Daffinee, Melrose, Mass.

Results of a Systematic Investigation of the Causes for a Temporary Increase in the Neurologic Complications of Diphtheria. W. Scheid, and H. Wieck, Schweiz. Arch. Neurol. u. Psychiat. **69**:269, 1952.

In Germany, as well as in other countries, there was a noteworthy increase in the neurologic complications of diphtheria during the later years of World War II and the years immediately following. The authors' material consisted of 2,292 cases of faucial diphtheria observed from

both the general clinical and the neurologic standpoint from 1946 to 1949. The respective percentages of neurologic complications for 1946 and 1947 were 25.5 and 27.3. Thereafter the percentage fell rapidly, reaching 4.2 in 1949. Neurologic complications developed in 76% of severe cases of diphtheria and in only 2% of the mild cases. A series of 1,110 cases coming under observation 4 days or less after onset of diphtheria and followed longer than 60 days were selected for more exhaustive study. In this group the frequency of neurologic complications likewise stood in direct proportion to the severity of the initial infection. In all the mild cases of diphtheria muscular weakness was limited to the throat. The extremities, on the other hand, became involved in only the severe and the moderately severe cases. In all but 3 of the 35 cases of severe polyneuritis there was a history of diphtheria of the severe type. These results tended to refute an older view that polyneuritis frequently develops after diphtheria of mild degree. Decreasing mortality rates corresponded with the progressive decline in the frequency of neurologic complications.

Results of clinical study and epidemiologic data indicated that neurologic sequelae had diminished in number because the morbidity rate of diphtheria had likewise fallen and cases of very severe faucial diphtheria had become rare. The authors found nothing to support the assumption that decreasing frequency of neurologic complications was due to improved living conditions. On the contrary, their results indicated that the diphtheritic toxin itself played the decisive role in the pathogenesis of neurologic complications.

DANIELS, Denver [A. M. A. Arch. Neurol. & Psychiat.].

FULMINATING POSTSCARLATINAL PURPURA, WITH THE RARE FINDING OF A MARKED HEPATIC PURPURA AT NECROPSY. G. SARDINI, Minerva pediat. **4**:276 (April 15) 1952.

A 5-year-old girl, two days after a tonsillectomy, had a high temperature and the rash of scarlet fever. The child's temperature and clinical condition did not respond well to penicillin. About nine days later, many petechiae were noted over the whole skin area, and soon afterwards ecchymoses and meningeal symptoms appeared, and the child died. A striking finding at autopsy was the purpuric mottling over the liver surfaces. Blood cultures were negative.

HIGGINS, Boston.

A CASE OF RELAPSING VARICELLA. M. MALASPINA, Minerva pediat. **4**:326 (April 30) 1952.

The patient was a 3-year-old girl in the hospital for severe infections involving the middle ear, the lymph nodes, and the lungs; she also had furunculosis. She had two typical attacks of chicken pox, while in the hospital, separated by a period of 21 days. On the fourth day of the first attack, another patient in the room with her came down with chicken pox. The question will arise whether the second attack was a relapse of the first or a reinfection.

HIGGINS, Boston.

A CASE OF COMPLETE HEART BLOCK IN DIPHTHERIA. H. M. C. POORTMAN and H. K. LANTING, Maandschr. kindergeneesk. **20**: 226 (Aug.) 1952.

The authors describe a case of complete heartblock following toxic diphtheria in a boy, 3 years of age, seen in Bandung (Indonesia), where diphtheria is rare and malignant diphtheria almost unknown.

FROM THE AUTHORS' SUMMARY.

Acute Infectious Diseases

COXSACKIE VIRUSES. CHARLES M. CARPENTER and RUTH A. BOOK, California Med. **77**:127 (Aug.) 1952.

Coxsackie disease comprises three clinical entities: herpangina, so-called nonparalytic poliomyelitis, and epidemic pleurodynia. Several strains of antigenically related viruses, Groups A and B, designated as Coxsackie virus, have been isolated from stool specimens and from material

from the throat of many patients with the diseases mentioned. Inasmuch as the virus has also been recovered from normal persons, there is as yet uncertainty as to causal relationship between the presence of the virus and the disease. Reports of the isolation of Coxsackie virus and poliomyelitis virus from the same patient make difficult the interpretation of the findings.

The diagnosis of Coxsackie disease entails animal inoculation and serologic procedures. Emphasis is placed on the necessity of obtaining stool specimens, throat washings, and "paired" blood specimens from patients suspected of having the disease.

PRYOR, Redwood City, Calif.

TREATMENT OF PINWORM INFECTION (ENTEROBIUS VERMICULARIS) WITH EGRESSIN. R. F. GODDARD, and H. W. BROWN, J. Pediat. **40**:469 (April) 1952.

Egressin is a thymol compound first synthesized in Germany. The dose for children is 1 gm. three times a day. It is effective against pinworms in approximately 40% of cases.

MACDONALD, Pittsburgh.

WETZEL GRID ANALYSIS OF RHEUMATIC CHILDREN. L. C. KAHN, G. BROWN, and D. GOLDRING, J. Pediat. **41**:47 (July) 1952.

The Wetzel grid is a device that may be used to measure success in the treatment of children with rheumatic fever.

MACDONALD, Pittsburgh.

COXSACKIE VIRUS (C-VIRUS) INFECTIONS. E. BERGER, E. FREUDENBERG, and F. BOULET, Ann. paediat. **179**:65 (Aug.) 1952.

Infection with Coxsackie virus can be achieved not only in newborn mice and hamsters but also in juvenile rats; these, however, do not present any clinical signs. The myositis in young rats corresponds histologically to that found in newborn mice. This proves that the C-virus may produce infections in juvenile rats which do not become manifest clinically.

In the early stage experimental infections can be produced in newborn mice by injecting blood, which shows that there exists in human cases a viremia, a fact emphasized also by other investigators.

Besides the course tyipcal in the animal experiment another very acute type is met with which manifests itself after a few hours. C-virus can produce infections which do not become clinically manifest in young rats after lactation. In adult mice, if the virus is injected in high dosage, apparent infection may develop. If the mother was infected before delivery, mice were either born dead or died within one to two days. They were found to suffer from spotted, partly generalized myositis, while in the mothers there were frequently found encephalitides.

FROM THE AUTHORS' SUMMARY.

THE IMPORTANCE OF COXSACKIE VIRUSES IN HUMAN DISEASE PARTICULARLY HERPANGINA AND EPIDEMIC PLEURODYNIA. ROBERT J. HUEBNER, M.D., EDWARD A. BEEMAN, M.D., ROGER M. COLE, M.D., PAUL M. BEIGELMAN, M.D., and JOSEPH A. BELL, M.D., New England J. Med. **247**:285 (Aug. 21) 1952.

It is apparent that Coxsackie viruses are among the most recently recognized agents of disease, and that physically and epidemiologically—though not pathogenetically nor immunologically—they resemble the viruses of poliomyelitis and may therefore occur with them under the same conditions, even in the same human host. They are among the most prevalent of recognized viruses; although they have not been found to cause death in human beings, they cause considerable misery and distress and are therefore of clinical as well as theoretical importance. The roles have not been determined for all these viruses but controlled studies have indicated that many of those known at present cause either herpangina or epidemic pleurodynia; there is no good evidence at present that in mixed infections they influence the course of

poliomyelitis. However, the significance of mixed infections requires more study. Beginning in early childhood inapparent and mixed infections with various types of Coxsackie viruses occur repeatedly; this very prevalence has forced a critical scrutiny of the criteria customarily used to establish the etiologic significance of human viral parasites and has necessitated new concepts of the viral "flora" of man. The comparative ease with which these agents can be isolated and handled in the laboratory provides an excellent opportunity for studying the basic nature of small viruses, new methods of mass sampling for viruses, and the epidemiology of viruses transmitted by similar routes.

WHEELOCK, Denver.

MYANESIN IN THE TREATMENT OF TETANUS. C. G. ALDERMAN, Clin. Rep. Adelaide Child. Hosp. **2**:107 (Nov.) 1951.

Eight patients with tetanus were treated with mephenesin (Myanesin) in addition to the usual routine methods. The drug was given by continuous intravenous drip and appeared to obviate the need for other sedatives. There were four recoveries.

MCGUIGAN, Evanston, Ill.

CLINICAL NOTES ON LAGRIPPE IN CHILDREN. JOSE ALFONSO RUIZ MARIN, Acta pediat. espan. **35**:422 (June) 1952.

The author describes the epidemiology, morbidity, and mortality of an epidemic of influenze (la grippe) in Cadiz in 1951 and 1952, with reference to children. In this epidemic, children in a given family had their illness before the adults. Children from 4 to 6 years had the largest number of sequelae. Children of this age, however, had shorter recovery time. The older children had the postinfection asthenia similar to that noted in the adults. The symptomatology and treatment are described. The most frequent complications were pneumonitis, pseudocroup (laryngotracheitis) and a few mild cases of bronchitis and otitis media. The epidemic was much milder in 1952 than in the preceding year.

ALLEN, San Francisco.

CHEMICAL AND CYTOLOGICAL STUDY OF THE CEREBROSPINAL FLUID IN POLIOMYELITIS. DELFIN PEREZ SANDOVAL, Acta pediat. espan. **35**:572 (July) 1952.

A study of the appearance, the alteration in the glucose, chlorides, proteins, globulins, and cellular content of the cerebrospinal fluid in 14 cases of poliomyelitis was made. The author says there are no findings characteristic enough to make a diagnosis, and that a sure diagnosis must be made clinically.

ALLEN, Santa Fe, N. Mex.

HUMAN INFESTATION WITH DIPYLIDIUM CANINUM. ENRIQUE FANTA NUNEZ, Rev. chilena pediat. **23**:393 (Sept.) 1952.

The first two cases of human infantile dipylidiasis in Chile are reported. Some considerations concerning the clinical aspects and etiologic agent of this disease are given.

FROM THE AUTHOR'S SUMMARY.

CONTRIBUTION TO THE KNOWLEDGE OF LEPTOSPIRAL DISEASES IN CHILDREN. WERNER STROBEL, Med. Klin. **47**:1415 (Oct. 24) 1952.

Over a period of three years, 17 cases of leptospirosis were observed in a children's hospital in a town of Northern Germany. The age of the children varied from 2 to 14 years. Weil's disease was noted in 13 cases and *Feldfieber* in four. Of the 13 children with Weil's disease, 11 were anicteric and in 8 of these a leptospiral meningitis was found by spinal puncture. Only one of these patients was free from any sign of meningism. The course of the meningitis varied considerably, and the clinical symptoms may extend to more than three weeks. Uveitis was seen in 8 of the 17 children on special ophthalmological examinations, usually in the third to fifth week, but in one it was seen on the ninth day of the disease. In one case a secondary turbidity of the lens developed. Therapeutic trials with streptomycin, penicillin, and chlortetracycline (aureomycin) were not encouraging.

AMBERG, Rochester, Minn.

CHANGES OF THE PROTEIN IN TYPHOID AND PARATYPHOID B. M. HERTEN, Ztschr. Kinderh. **70**:300, 1952.

Electrophoretic studies of the protein components during typhoid showed a lowering of the albumin and increase of the α globulin fraction at the onset of the disease and an increase in the γ globulin fraction beginning with the 10th to the 14th day, the degree of the changes depending upon the severity of the illness. Patients with light infections carrying bacteria for a long time in the stools also showed a marked increase in γ globulin. The increase in the γ globulin fraction is caused by the increase of antibodies in the blood, but not all these antibodies were specific. The Gruber-Widal reaction did not run parallel with the γ globulin curve; a definite explanation for this phenomenon is still lacking.

Treatment with chloramphenicol (Chloromycetin) did not interfere with the γ globulin increase; although it shortened and eased the course of the disease, the task of forming antibodies remained with the organism.

In cases of liver damage due to typhoid the albumin fraction was particularly low and the γ globulin fraction correspondingly high (35 to 40%)—much higher than usually caused by antibody formation.

GLASER, Jerusalem.

Chronic Infectious Diseases

HISTOPATHOLOGY OF EXPERIMENTAL HISTOPLASMOSIS. G. F. KIPKIE and ARDEN HOWELL JR., A. M. A. Arch. Path. **51**:312 (March) 1951.

Histological studies were performed on a total of 491 male and female mice after intracerebral, intravenous, and intraperitoneal injection of various strains of Histoplasma capsulatum. Regardless of the route of inoculation, the liver and spleen were most commonly involved. When correlated with the various routes of injection, the distribution of the lesions would seem to bear a direct relation to the number of parasites entering the general circulation. The most widespread lesions were noted in animals in which the fungus was injected intravenously. Organisms suspended in mucin were injected intraperitoneally, but it was not possible to state whether mucin had a protective action on the fungus cells in inhibiting their destruction.

HAW CHAN, San Francisco.

TREATMENT OF TUBERCULOUS MENINGITIS WITH CORTISONE AND STREPTOMYCIN. S. J. SHANE, R. A. CLOWATER, and C. RILEY, Canad. M. A. J. **67**:13 (July) 1952.

The authors report a case of tuberculous meningitis in which the addition of cortisone to the regimen appeared to be lifesaving.

MCGUIGAN, Evanston, Ill.

RESISTANCE TO TUBERCULOSIS IN DOGS VACCINATED WITH BCG AND WITH KILLED BACILLI. P. SALVIOLI, A. DEGLI ESPOSITI, and M. A. DINA, Presse méd. **41**:1508 (Nov. 8) 1952.

The authors, after comparing clinically and roentgenologically the pulmonic changes in dogs experimentally infected with tuberculosis, describe the differences between the animals which had been vaccinated and those which had not been. The antituberculosis vaccination had been conducted in various groups of dogs with the use of BCG, AIP (anatuberculin integral Petragnani) and VDS (Vaccine of Diffusion Salvioli) prepared from killed bacilli. The nonvaccinated dogs died spontaneously of tuberculosis and showed many specific pulmonic and lymphoglandular lesions. The vaccinated dogs, especially those which were vaccinated with killed bacilli, at autopsy exhibited but few lesions. There was a high percentage of mild lesions (fibrous changes, productive nodules, allergic foci).

The authors point out that an essential condition for the efficacy of the vaccination, whatever the vaccine used, is an adequate dose and an adequate technique so that at the vaccination focus there may properly develop a minor harmless tuberculosis which is the basis of resistance of the organism against the actual tuberculous disease.

FROM THE AUTHORS' SUMMARY.

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS AT PUBERTY AND IN ADOLESCENCE. H. WISSLER, Bull. Schweiz. Akad. Med. Wissensch. **8**:356 (July) 1952.

Thirty-one patients with pulmonary tuberculosis in puberty (11 with open noncavernous disease and 20 with cavitation) were treated with streptomycin for an average period of 69 days. In 23 there was a good roentgenological regression; in 10 of the 20 with cavitation the cavities remained closed for a minimal observation period of one year, and in four cases the success of the therapy was only temporary.

FROM THE AUTHOR'S SUMMARY.

MONILIASIS. R. AMLIE, Ann. paediat. **179**:316 (Nov.) 1952.

The author presents observations on a fatal Monilia infection. Three facts are outstanding: 1. Antibiotic treatment favors fungous infections, without any doubt. 2. The fungi are not visible in histological paraffin-embedded slides. 3. It appears that the fungous toxins produce a rapid decrease of the lymphocytes in the circulating blood.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF NECK AND HILUS GLAND TUBERCULOSIS WITH ISONIAZID. H. WISSLER, Helvet. paediat. acta **7**:550 (Dec.) 1952.

A series of 13 patients with glandular tuberculosis of the neck were treated with isoniazid followed by extirpation of the glands. Neither a histological nor a bacteriological effect could be observed. In four cases of tumerous tuberculous hilar glands, three times a visible regression could be seen while in four cases of "epituberculosis" there was no change.

FROM THE AUTHOR'S SUMMARY.

ISONIAZID (RIMIFON) IN EXPERIMENTAL TUBERCULOUS MENINGITIS. B. FUST and A. STUDER, Helvet paediat. acta **7**:558 (Dec.) 1952.

To test the therapeutic application of isoniazid in tuberculous meningitis, rabbits were given lethal doses of tubercle bacilli of the bovine type (Vallee strain) intracisternally and treated with isoniazid in three different experiments.

When isoniazid was given after the appearance of unmistakable symptoms of meningitis, the effect was only transitory. All 12 rabbits died, on the average sooner than the nontreated control animals. The cause of death was estimated to be the specific infection in only one-third of the experimental animals, while the death of the remaining two-thirds was due to the increased toxicity of isoniazid for animals with meningitis [there are as yet no indications as to whether these conditions can be applied to human beings] and probably also to a Herxheimer-like reaction.

The same result was obtained in the prohpylactic-therapeutic experiment on two rabbits when treatment was commenced toward the end of the minimum incubation period.

In a simultaneous experiment with treatment commencing on the day after intracisternal infection all eight animals survived and showed constant gain in weight. The animals were given 10 mg. of isoniazid per kilogram of body weight daily divided into 2 subcutaneous doses, morning and afternoon. Four rabbits which had been treated for 90 days were still alive one and one-half months after the treatment had been discontinued.

All the control animals died of the intracisternally induced tuberculosis. The clinical course and the pathological and histological findings in these animals are described in detail.

FROM THE AUTHORS' SUMMARY.

VACCINATION AGAINST TUBERCULOSIS BY THE MULTIPLE PUNCTURE METHOD USING PETRAGNANI'S ANATUBERCULIN. G. BUONOMINI, L. POLI and G. SANTOPADRE, Clin. pediat. **33**:749 (Dec.) 1951.

The multiple puncture method of Mazzetti calls for about 80 practically simultaneous needle punctures of the skin of the arm through a 20 to 50% mixture of Petragnani's anatuberculin and either a pomade or polyvinyl pyrrolidone (Subtosan). The effectiveness of this vaccination

procedure was studied on 25 children. Tuberculin tests were positive 12 months after the vaccination. There were no untoward incidents, no ulceration, and no large scars from this procedure. The children's growth and general health were unimpaired. Preference was expressed for the 50% anatuberculin-polyvinyl pyrrolidone preparation.

HIGGINS, Boston.

SPINAL ARACHNOIDITIS IN THE COURSE OF TUBERCULOUS MENINGITIS BEING TREATED BY STREPTOMYCIN. S. LO BIANCO, Lattante **23**:465 (Aug.) 1952.

Case histories with necropsy findings of four children with tuberculous meningitis with spinal block and arachnoiditis are given. The conclusion is drawn that the arachnoiditis is due to the spread of the tuberculous process and not due to the administration of the streptomycin.

HIGGINS, Boston.

THREE YEARS EXPERIENCE IN THE TREATMENT OF TUBERCULOUS MENINGITIS WITH STREPTOMYCIN. M. L. QUARTI and A. VERGA, Minerva pediat. **4**:310 (April 30) 1952.

From January, 1947, to July, 1950, 123 children with tuberculous meningitis were treated with streptomycin in the pediatric clinic of the University of Milan. In 1947, all the patients died, but after that year better methods of treatment have led to the recovery of 42% of the patients. The mortality was 88% for infants under 1 year of age, 68% for infants 1 to 2 years old, 48% for children 2 to 6 years old, and 32% for children 6 to 13 years old. Tubercle bacilli were found by smear or by inoculation of guinea pigs in the spinal fluid of all of the 38 cured patients. The hospital stay of these 38 patients varied from 107 to 483 days, streptomycin being given daily intrathecally over periods from six weeks to six months.

HIGGINS, Boston.

HEMORRHAGIC SYNDROMES IN TUBERCULOSIS. G. ROTTINI, Minerva pediat. **4**:565 (July 15) 1952.

Two cases of purpura in tuberculous children are reported with autopsy findings. An 11-year-old girl had a transitory purpura, apparently due to an abnormality of the megakaryocytes in the bone marrow. A 2-year-old girl had purpura, apparently due to capillary fragility.

Purpura in tuberculosis is classified into four types, in each of which there is a varying degree of toxicity of the capillary wall cells. The types are (1) that due to capillary toxicosis without platelet disturbance, (2) that due to pathology of the platelets without thrombopenia, (3) that due to a temporary thrombopenia, and (4) that with miliary involvement of the bone marrow and a persistent thrombopenia.

HIGGINS, Boston.

EXPERIENCE IN THE TREATMENT OF CHILDHOOD TUBERCULOSIS WITH ISONIAZID. T. PORCELLI, Minerva pediat. **4**:582 (July 31) 1952.

In a three-month experience with the use of isoniazid in treating various types of childhood tuberculosis in the Children's hospital in Milan, the author obtained excellent clinical results, although little change in the x-ray picture was noted.

HIGGINS, Boston.

HISTOPLASMOSIS IN CHILDREN. F. N. SILVERMAN and J. SCHWARZ, Rev. chilena pediat. **23**:225 (June) 1952.

Common aspects are given on the epidemiology, mycology, pathology, and laboratory diagnostic techniques of histoplasmosis in infancy. Several illustrative cases (fatal and nonfatal) of histoplasmosis in children are described, and the clinical and roentgenological characteristics are briefly discussed.

FROM THE AUTHORS' SUMMARY.

INTRASPINAL INJECTIONS OF A MIXTURE OF STREPTOMYCIN, SOLVOTEBEN, AND P. A. S. OVER LONG PERIODS: AN IMPROVEMENT IN THE TREATMENT OF TUBERCULOUS MENINGITIS IN CHILDREN. FRITZ HEEPE and THEODOR SANTELMANN, Med. Wchnschr. **76**:1015 (Aug. 17) 1951.

The following routine treatment of children with tuberculous meningitis was adopted. Streptomycin is given intramuscularly twice daily in a dosage of 12.5 mg. per kilogram for seven months. Paraaminosalicylic acid is given by mouth in a dosage of 0.3 gm. per kilogram daily for five days. It is stopped for two days. This regimen is adhered to up to the seventh month. A mixture of streptomycin-Solvoteben (a thiosemicarbazone compound) and paraaminosalicylic acid is given daily in the first, second, third, fifth, and seventh months. In severe cases it may be administered daily in the ninth and eleventh months. If necessary, intracisternal injections of streptomycin and Solvoteben may be given under special precautions. Directions are given for the preparation of the mixture and for its dosage. Twenty children, $2\frac{1}{2}$ to 11 years of age, were treated. Of these, 16 were probably cured.

AMBERG, Rochester, Minn.

SCLERODERMA, VITILIGO, AND TUBERCULOSIS. H. RIES, Ztschr. Kinderh. **70**:125, 1951.

After discussing the definition and various theories of scleroderma, Ries reports two cases in which active tuberculosis was present at the time of the appearance of the local sclerodermic lesions. He believes that the skin changes are on a neurogenic (sympathetic) basis, the stimulus for which originates in the diencephalon. The changes in the diencephalon are supposedly caused by infectious diseases, in the presented cases by tuberculosis.

GLASER, Jerusalem.

COMPARATIVE STUDIES OF SABIN-FELDMAN'S COLOR TEST FOR TOXOPLASMOSIS AND THE TOXOPLASMIN TEST. O. VIVELL, Ztschr. Kinderh. **70**:271, 1952.

The Sabin-Feldman color test was compared with the toxoplasmin skin test in 129 adults and children. Toxoplasmin was produced from peritoneal exudate of mice. There was almost complete correlation between the results of the two tests except for some infants under 6 months of age, in whom the color test was positive at various titers but the skin test negative. This discrepancy between the two tests can be explained possibly by the passive transfer of antibodies from the mother to the child, giving a positive color test titer but a negative skin test.

The results of Sabin and Feldman, who did not find such close correlation between the two tests but did find a high number of negative skin tests in the presence of positive color tests, are explained by Vivell as due to the fact that Sabin and Feldman used toxoplasmin obtained from egg cultures which does not seem reliable.

The author recommends the skin test as reliable for screening examinations and the Sabin-Feldman color test for quantitative evaluation of the course of antibody formation.

GLASER, Jerusalem.

CHANGES IN THE ELECTROENCEPHALOGRAM IN TUBERCULOUS MENINGITIS DURING STREPTOMYCIN THERAPY. R. GARSCHE and G. DLUGOSCH, Ztschr. Kinderh. **70**:354, 1952.

The authors conclude that the changes in the electroencephalogram in tuberculous meningitis are not specific and have no prognostic significance, but that the severity of the cerebral damage is reflected in the electroencephalogram and that in acute meningitis improvement of the electroencephalographic curve can be noted as a result of streptomycin therapy. In chronic meningitis, however, the influence of streptomycin is not noticeable in the electroencephalographic curve.

GLASER, Jerusalem.

CHEMOTHERAPY OF TOXOPLASMOSIS. MATHILDE L. M. HOUBEN, Maandschr. kindergeneesk. **20**:213 (Aug.) 1952.

In the treatment of experimental toxoplasmosis, several sulfones have a therapeutic action. These agents work probably by the liberation of diaminodiphenyl sulfone in the intestinal tract. A trial of these agents in human toxoplasmosis should be considered.

FROM THE AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels, and Spleen

CONGENITAL PULMONIC STENOSIS WITH OPEN FORAMEN OVALE IN INFANCY. R. P. JOHNSON, and ELOISE E. JOHNSON, Am. Heart J. **44**:344 (Sept.) 1952.

Five cases of congenital valvular pulmonic stenosis with open foramen ovale occurring in infants and proved by autopsy are reported. The patients were all girls, and their ages were 3, 4, 9, 12, and 19 months. This malformation may prove to be the second commonest cause of cyanotic congenital heart disease, only the tetralogy of Fallot occurring more frequently.

The syndrome in infants includes early cyanosis, often present at birth, which may clear for a short period, only to return. Polycythemia and clubbing of the fingers and toes may follow the cyanosis. A precordial systolic murmur of slight to loud intensity is present. Dyspnea in these infants occurs in paroxysms and is a warning of approaching dissolution, which may be prevented by a timely surgical valvulotomy. The heart is enlarged and has a characteristic roentgen appearance of an upturned apex, a dilated pulmonary artery, and avascularity of the peripheral lung fields. The electrocardiogram shows marked right ventricular hypertrophy and the P waves are prominent in Lead II.

This syndrome is to be differentiated from pure (isolated or uncomplicated) pulmonic stenosis and from the tetralogy of Fallot. The common "blue baby" operations of Blalock or Potts are not beneficial in pulmonic stenosis with open foramen ovale.

FROM THE AUTHORS' SUMMARY.

CONGENITAL HEART DISEASE: AN ANALYSIS OF ELECTROCARDIOGRAPHIC PATTERNS IN FORTY-FOUR PATIENTS WITH ELEVATED RIGHT VENTRICULAR PRESSURE. R. S. COSBY, D. C. LEVINSON, W. J. ZINN, S. P. DIMITROFF, and G. C. GRIFFITH, Am. Heart J. **44**:581 (Oct.) 1952.

The authors reported the electrocardiographic findings on 44 patients with congenital heart disease who on cardiac catheterization showed a right ventricular systolic pressure of 30 mm. Hg or above.

Thirty-five of the patients who had structurally predominant right ventricular hypertrophy showed either the classic electrocardiographic pattern of right ventricular hypertrophy or varying degrees of incomplete right bundle-branch block. Of nine patients with structural involvement of both right and left ventricles, six showed electrocardiographic evidence of bilateral hypertrophy.

The authors point out the importance of electrocardiography in congenital heart disease with right ventricular hypertrophy.

GIBSON, Chicago.

POSITION OF AORTIC ARCH AND DESCENDING AORTA: ROENTGENOLOGIC SIGNS IN CHILDHOOD. RACHEL ASH, Am. J. Roentgenol. **67**:924 (June) 1952.

The position of the aortic arch is important in the surgical approach in cases in which cyanotic heart disease can be treated by the creation of an artificial patent ductus. An error in diagnosis, resulting in entrance of the chest of a young infant on the side opposite to the descending aorta, might prove fatal.

Characteristically the right aortic arch produces a deviation of the trachea and esophagus to the left, in the region of the aortic arch. Deviation of the trachea to the right would indicate a left aortic arch, probably associated with a left descending aorta, and deviation of the trachea to the left would indicate a right aortic arch, probably with a right descending aorta. Retroesophageal crossing of the aorta occurs very rarely.

HODGSON, Rochester, Minn.

BRAIN HEMORRHAGE AFTER CAROTID-JUGULAR ANASTOMOSIS. I. M. TARLOV, and D. GRAYZEL, Ann. Surg. **136**:250 (Aug.) 1952.

Beck, McKhann, and Belnap attempted to increase the blood supply of the brain and thus benefit mentally and physically retarded children. They established a fistula between the common or the external carotid artery and the internal jugular vein.

The authors performed this operation on nine children. Not only did the operation fail to achieve the desired result, but serious complications followed. These were severe proptosis, and subarachnoid hemorrhage in two patients, who recovered when the anastomosis was interrupted. Because of the progressive dilatation of the intracranial veins, the authors suspected that other complications might occur later. This suspicion was confirmed by the case of a fatal massive intracerebral hemorrhage that occurred five months after the left external carotid artery was anastomosed to the left anterior jugular vein in a retarded child. The case report is given in detail.

BANTIN, Omaha.

CEREBRAL LESIONS IN CONGENITAL HEART DISEASE. M. BERTHRONG and D. C. SABISTON JR., Bull. Johns Hopkins Hosp. **89**:384 (Nov.) 1951.

Berthrong and Sabiston reviewed the autopsy findings in 162 cases of serious congenital heart disease, 135 of the cyanotic and 27 of the acyanotic type, with special regard to the occurrence of all types of cerebral lesions, and attempted to determine, if possible, the pathogenesis of such lesions.

They found that cerebral lesions of different types occur with greatly increased frequency in patients with congenital heart disease. In patients with cyanotic heart disease, including those who have had surgical procedures, cerebral infarctions are particularly common, occurring in 25 of the 135 cases. Cerebral necroses, as a result of the greatly impaired tissue oxygenation without vascular occlusions, may account for a relatively small number of cases of microscopic lesions. The majority of the infarcts are the result of vascular occlusions.

The authors emphasize the important role of polycythemia in the production of intravascular thromboses as a cause of infarcts and discuss the close similarity in this respect of these cases to cases of polycythemia vera in adults.

Both arterial and venous cerebral thromboses occur. It is not known whether the thromboses leading to the arterial occlusions usually develop in peripheral veins, to reach the cerebral arteries as paradoxical emboli through cardiac defects, or form in the cardiac chambers to embolize the brain, or develop in situ in the cerebral arteries; but all mechanisms may occur. Venous thrombi which are seen or are inferred to exist from hemorrhagic infarctions are more common than arterial occlusions.

The severe surgical procedure necessary for the alleviation of these cardiac malformations imposes the additional factors of shock and hemoconcentration on the already increased tendency to thrombosis. Hemorrhagic infarctions are particularly frequent in the immediate postoperative period. The authors note the part played by the common attacks of increased cyanosis and fainting in increasing the tendency to thrombosis by further reducing the rate of cerebral blood flow.

Brain abscesses also occur with increased frequency in patients with cyanotic heart disease.

Patients with acyanotic heart disease also present many cerebral lesions, but these are often of a nonthrombotic origin or, when they are due to thrombosis, causes for such thromboses are obvious. A very high incidence of congenital aneurysms of the circle of Willis in patients with coarctation of the aorta is reported.

ALPERS, Philadelphia [A. M. A. Arch. Neurol. & Psychiat.].

BACTERIAL ENDOCARDITIS AFTER A TAUSSIG-BLALOCK OPERATION IN A CASE OF UNUSUAL PATHOLOGY. H. EVERLEY JONES and E. G. DOLTON, Arch. Dis. Childhood **27**:157 (April) 1952.

A case is described in which infective endocarditis caused death by rupture of a mycotic aneurysm of the pulmonary artery two and one-half years after a Taussig-Blalock operation had been performed. Postmortem examination showed that the heart was functionally bilocular and that there was transposition of the great vessels.

KELLY, Milwaukee.

Diseases of Lungs, Pleura, and Mediastinum

CONGENITAL CYSTIC DISEASE OF THE LUNG IN NEWBORN. FRANK B. WHITESELL JR., and WILLIAM J. WHITE, Ann. Surg. **136**:299 (Aug.) 1952.

Cystic disease of the lungs in the neonatal period has not been adequately emphasized. Prompt recognition of this relatively rare disease and an aggressive surgical attitude toward it may prevent an otherwise fatal outcome.

Diagnosis of this disease can be made with ease if routine chest roentgenograms are obtained in every instance of neonatal respiratory distress.

The treatment of choice is radical extirpation of the diseased lung tissue by lobectomy or pneumonectomy, both of which are well tolerated even in the first few days of life.

BANTIN, Omaha.

SURGICAL CORRECTION OF FUNNEL CHEST. F. GORDON KING, Ann. Surg. **136**:798 (Nov.) 1952.

Six cases of surgically treated funnel chest deformity are reported. Results in all cases were excellent, and there were no serious complications, residuals, or deaths. The period of observation covered two to four years. There is no indication that recurrence is likely. The substernal ligament has not seemed an important factor in these cases.

BANTIN, Omaha.

A NONTOXIC DETERGENT FOR AEROSOL USE IN DISSOLVING VISCID BRONCHOPULMONARY SECRETIONS. JOSEPH B. MILLER and EDWARD H. BOYER, J. Pediat. **40**:767 (June) 1952.

Triton A-20 is an alkylaryl polyether alcohol. It is a valuable detergent with little or no pulmonary toxicity. In the form of an aerosol, it effectively liquefies sputum.

MACDONALD, Pittsburgh.

MAXIMUM BREATHING CAPACITY AND VITAL CAPACITY OF MALE CHILDREN AND ADOLESCENTS. B. G. FERRIS JR., J. L. WHITTENBERGER, and J. R. GALLAGHER, Pediatrics **9**:659 (June) 1952.

Expected mean values and a range of normal values (± 2 standard deviations) are presented for the vital capacity and the maximum breathing capacity of male children and adolescents.

It is recommended that calculations of the above values be based upon four attributes (age, height, weight, and body-surface area) rather than upon a prediction deriving from a single attribute (especially in a boy who does not have a standard height and weight for his age.)

FROM THE AUTHORS' SUMMARY.

GIANT CELL PNEUMONIA WITH INCLUSIONS. RUSSELL W. WELLER, Pediatrics **10**:681 (Dec.) 1952.

A case of giant cell pneumonia with inclusions is reported. Intracytoplasmic and intranuclear inclusions are present. Exhaustive search reveals no inclusions in viscera other than the lungs. The pulmonary cytologic picture is similar to that seen in canine distemper.

FROM THE AUTHOR'S SUMMARY.

COMPARATIVE STUDY OF CANINE DISTEMPER AND A RESPIRATORY DISEASE OF MAN. JOHN M. ADAMS, Pediatrics **11**:15 (Jan.) 1953.

Clinical, epidemiologic, pathologic, and serologic evidence has been presented which indicates a possible relationship of canine distemper and a respiratory disease of human beings.

Neutralization of distemper virus infection in ferrets has been accomplished experimentally; infection caused by this virus in living chick embryos has been neutralized by human sera and by human gamma globulin. Both in vivo and in vitro methods were employed in these experiments.

Inclusion bodies with the same morphologic and staining characteristics are shown in the two diseases, and there are similar tissue reactions to infection. The striking features of these changes are the proliferation and destruction of pulmonary lining epithelium, giant cell formation, and a predominant mononuclear reaction in the animal and human sections.

A review of the literature on a possible relationship between canine distemper and human illness has been presented. The former disease is now proved to be due to a specific virus.

From the Author's Summary.

Natural Regression of Pulmonary Cysts During Early Infancy. John Caffey. Pediatrics **11**:48 (Jan.) 1953.

The immediate and ultimate prognosis of surgically untreated pulmonary and pleural cysts is excellent, even during the early weeks of life.

From the Author's Summary.

Respiratory Administration of Chloramphenicol in Children. M. Gomirato Sandrucci, Minerva pediat. **4**:258 (April 15) 1952.

Chloramphenicol was given to healthy children, 5 to 10 years of age, by three different routes: (1) by mouth, (2) by rectum, and (3) by inhalation. The breathing of a nebulized solution of the drug led to as satisfactory absorption as was obtained by the other routes, as indicated by blood and urine levels.

Higgins, Boston.

Visualization of Hilar and Mediastinal Glands by Means of Posterior Mediastinal Pneumography and Stratigraphy. P. Durand, E. de Toni, and G. Porro, Minerva pediat. **4**:303 (April 30) 1952.

Roentgenograms are shown which illustrate the value of the injection of air into the anterior and posterior mediastinum for the depiction of enlarged lymphatic and thymic glands. Some of the films were taken by stratigraphy.

Higgins, Boston.

Note on Differential Diagnosis of Congenital Pulmonary Cysts. E. Kratkova, Pediat. listy **7**:349 (Dec.) 1952.

This is a description of four cases of congenital pulmonary cysts found in girls; two of them were successfully operated on. Tomography, bronchography, and thoracoscopy will confirm the diagnosis. A differential diagnosis among the pulmonary cyst, pulmonary abscess, pneumothorax, and emphysema bullosum is usually difficult, but an x-ray examination and prolonged observation will make the diagnosis clear. Operative treatment is being recommended.

From the Author's Summary.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

The Effect of Aureomycin and Chloramphenicol on the Fungal and Bacterial Flora of Children. J. J. McGovern, R. H. Parrott, Chester W. Emmons, Sidney Ross, F. G. Burke, and E. Clarence Rice, New England J. Med. **248**:397 (Mar. 5) 1953.

One hundred normal children were examined to determine the incidence of "Candida albicans" in the gastrointestinal tract. This organism could be demonstrated in small numbers in the mouths of 14% of the children and in the rectum in 6%.

Twenty-one normal children were given chlortetracycline (aureomycin) orally for 8 days, and 24 children were given chloramphenicol intramuscularly or orally for 10 to 14 days. Laboratory and clinical observations were made on each child before, during, and after the treatment period. No clinical thrush was observed.

Before treatment the incidence of C. albicans in the gastrointestinal tract was 17% in this group of 45 children, rising to 33% at the end of the treatment period. By the third to the

eighth day of treatment, the average number of colonies of C. albicans had increased from 3 to 50. There was a marked decrease in Gram-negative and Gram-positive organisms in the gastrointestinal tract, with a concomitant increase in the fungal floras, including yeasts and various species of Candida other than C. albicans. FROM THE AUTHORS' SUMMARY.

CHEMICAL COMPARISON OF NORMAL MECONIUM AND MECONIUM FROM A PATIENT WITH MECONIUM ILEUS. DOROTHY J. BUCHANAN and S. RAPOPORT, Pediatrics **9**:304 (March) 1952.

A series of chemical analyses comparing normal meconium with meconium from a patient with meconium ileus demonstrated the following differences: (1) Normal meconium contained over four times the amount of total reducing sugar found in the meconium from a patient with meconium ileus; (2) normal meconium contained less total nitrogen, mostly nonprotein, than meconium from a patient with meconium ileus, which was mostly protein in nature, and (3) the phosphorus and purine contents were minimal in both samples.

About 15% of the reducing sugar of both the normal and the abnormal meconium was dialyzable.

Ammonium sulfate fractionation of normal meconium gave definite precipitates at a saturation of 83% and at complete saturation. Meconium from a patient with meconium ileus gave precipitates at saturations of 67 and 75%.

Alcohol fractionation of normal meconium gave precipitates at alcohol concentrations of 46, 50, 60, 67, 75, and 83%, reducing sugar to nitrogen rations rising from 3.2 to 6.6 with increasing alcohol concentrations. Alcohol fractionation of meconium from a patient with meconium ileus gave precipitates at alcohol concentrations of 56, 62, 66.5, and 81%, the reducing sugar to nitrogen ratios rising from 0.47 to 0.86 with increasing alcohol concentrations.

The action of pepsin and trypsin on normal meconium was not significant; on meconium from a patient with meconium ileus trypsin increased the per cent of nonprotein nitrogen twice and of pepsin sixfold. The reducing sugar to nitrogen ration of meconium from a premature infant was shown to increase as it progressed down the intestinal tract.

FROM THE AUTHORS' SUMMARY.

INFECTIVE GANGRENE OF THE MOUTH (CANCRUM ORIS). D. B. JELLIFFE, Pediatrics **9**:544 (May) 1952.

The clinical features of infective gangrene of the mouth are described as seen in malnourished children in Ibadan, Nigeria. The etiology is discussed with reference to malnutrition in general and seasonal food shortage in particular. Successful treatment with a remarkable degree of natural healing occurred with penicillin and a high protein diet.

FROM THE AUTHOR'S SUMMARY.

ADRENOCORTICAL TUMOR ARISING IN THE LIVER OF A THREE YEAR OLD BOY WITH SIGNS OF VIRILISM AND CUSHING'S SYNDROME. LAWSON WILKINS, and MARK M. RAVITCH, Pediatrics **9**:671 (June) 1952.

A case is reported of a boy 3 years 9 months of age, who presented the features of the adrenogenital syndrome. Roentgenograms showed a large calcified mass in the right upper quadrant of the abdomen. This proved to be a virilizing adrenocortical tumor, buried in the right lobe of the liver and receiving its circulation throughout the liver. Resection of four costal cartilages gave direct access to the liver through a transverse abdominal incision without the necessity for division of the diaphragm and permitted successful removal of the tumor and most of the right lobe of the liver. The tumor had no attachments to the right kidney or vena cava. There was no adrenal tissue in the usual location on the right. The child is well and developing normally two years after operation. FROM THE AUTHORS' SUMMARY.

USE OF I^{131}-LABELED PROTEIN IN THE STUDY OF PROTEIN DIGESTION AND ABSORPTION IN CHILDREN WITH AND WITHOUT CYSTIC FIBROSIS OF THE PANCREAS. PAUL S. LAVIK, LEROY W. MATTHEWS, G. W. BUCKALOO, SAMUEL SPECTOR and HYMER L. FRIEDELL, Pediatrics **10**:667 (Dec.) 1952.

A method is described for the evaluation of protein digestion and absorption by measuring the fecal excretion of isotope after the administration of a test meal of I^{131}-labeled protein. Application of this method to 10 children without gastrointestinal disease and to 5 with cystic fibrosis of the pancreas revealed the following facts: (1) less than 6% of the ingested isotope was excreted in the feces of the "control" subjects; (2) a 10 to 40% (average 22.5%) fecal excretion of the ingested isotope occurred in the children with cystic fibrosis of the pancreas; (3) a 50% decrease in the fecal excretion of isotope resulted in two of four children with cystic fibrosis of the pancreas when pancreatin was fed with the test meal; (4) one patient with cystic fibrosis of the pancreas, who after receiving pancreatin still excreted 40% or more of the ingested isotope in the feces, excreted only 8% when the test was repeated with prehydrolyzed protein.

FROM THE AUTHORS' SUMMARY.

CORROSIVE STRICTURES OF THE ESOPHAGUS AND THEIR TREATMENT. MERCER G. LYNCH, Selected Writings of the Ochsner Clinic **8**:24 (Dec. 31) 1949.

Lynch states that the numerous methods of treating corrosive strictures of the esophagus have met with varying degrees of success, but, despite legislation requiring labeling of all caustic substances and despite the fact that lye as a household agent is much less popular than formerly, strictures of the esophagus produced by lye still occur too often.

He reports three cases with roentgenograms. Details are given in the first 24 hours of the acute stage, when the pediatrician or internist first sees the patient, after which the otolaryngologist must plan an exact management of the case.

Retrograde esophagoscopy with through-and-through passage of the string is not an easy task and often is a risky procedure. Accomplishment of this step, however, marks a distinct milestone in the progress of the patient. Passage of the bougie from above for the first time is accomplished by means of the fluoroscope, which is safe. Progress is slow. In longitudinal stricture dilatations just about "hold their own." Deep burns of the esophagus cause dense scar tissue, and this requires repeated dilatations indefinitely. Where the burn is so extensive that even a filiform catheter cannot be passed, gastroesophagoscopy is the only method that will enable the patient to return to a normal mode of life.

GORDON, Philadelphia [A. M. A. Arch. Otolaryng.].

PATHOGENESIS OF RECURRENT ABDOMINAL PAIN IN CHILDHOOD. L. MALDAGUE, Acta paediat. belg. **6**:53, 1952.

In discussing the problem of recurrent abdominal pains in childhood Maldague describes the cases of three children, 11, 12, and 13 years of age, who complained of severe periodic cramps in the abdomen, in one preceded by severe headache. Since medical treatment was of no avail and the pains were intolerable, laparatomy was performed and visible peristaltic disturbances were seen during operation—in one case, small invaginations of the intestines at three different places which could be reduced easily. In two cases the laparatomy was sufficient to free the patient of symptoms, whereas the third child continued to have complaints.

The author feels that the basis for these peristaltic disorders is emotional disturbances and advocates psychotherapy. He feels that the results obtained by laparotomy were also psychological.

GLASER, Jerusalem.

CIRRHOSIS IN A 2 AND A HALF YEAR OLD CHILD WITH AN UNUSUAL CLINICAL COURSE AND WITH AN UNUSUAL PATHOLOGICAL FINDING. JAN SUMBERA and MAX DLUHOS, Pediat. listy **6**:46, 1951.

The authors describe a case of cirrhosis in a 2½-year-old child, which was localized in a part of the left lobe of the liver. The disease was diagnosed one year before the death of the

child by help of the puncture, and of the cirrhosis nodus in the left lobe. Pathologically this was a special kind of cirrhosis with cavernous dilatation of the bile ducts and with a strong adenomatous growth.

FROM THE AUTHORS' SUMMARY.

Nervous Diseases

BRAIN ABSCESS—OTOGENIC AND RHINOGENIC. B. H. SHUSTER, A. M. A. Arch. Otolaryng. **56**:114 (Aug.) 1952.

At present most intracranial complications of otolaryngologic origin are associated with chronic, rather than acute, infection of the ear or sinuses. Among the intracranial complications of ear and nose infections, brain abscess is probably as common as any of the others, and Shuster considers this subject in the present paper.

He first points out that the otolaryngologist who first sees the patient should keep the possibility of such a complication in mind and learn to recognize it. Of the signs or symptoms of brain abscess the most striking is probably the mental status of the patient. He is listless and unmindful of his surroundings. The characteristic headache is dull and thumping. The pulse rate is usually slow, and an elevation of temperature may occur with a subnormal pulse. Mild papilledema may be present. There may be a moderate increase in cell count of the spinal fluid.

In looking for localizing signs, the otolaryngologist should be acquainted with the anatomic features in the areas usually involved. The temporal lobe, the cerebellum, and the frontal lobe are the areas involved when the ear or sinuses are the etiologic factors. The temporal lobe is the commonest site. The author outlines points helpful in localization.

The treatment is surgical, and Shuster feels that the otolaryngologist, rather than the neurosurgeon, is best suited to continue the care of the patient and treat the abscess from the feeding point in the mastoid or sinus. From his experience, he finds that as soon as the abscess is diagnosed and localized, incision, drainage, and the insertion of a rubber tube constitute the simplest and most satisfactory method of treatment.

ALPERS, Philadelphia [A. M. A. Arch. Neurol. & Psychiat.].

NEW TREATMENT FOR HEREDITARY (HUNTINGTON) CHOREA. D. GOLDMAN, Am. J. M. Sc. **224**:573 (Nov.) 1952.

Six patients with Huntington's chorea were treated with procaine amide hydrochloride. Treatment was begun with 0.25 gm. four times a day and gradually increased over a two- to four-week period until 1.0 gm. four to five times a day was being administered. All patients had mild to marked reductions in the severity of the chorea, but there was no improvement of the patients' mental status. The side-reactions of the treatment consisted of faintness, somnolence, paresthesia in the extremities, and dryness of the mouth. Patients with paralysis agitans and myoclonic tics were not benefited.

BERLIN, Mount Vernon, N. Y. [A. M. A. Arch. Neurol. & Psycshiat.].

SEPARATION OF THE BLOOD VESSELS FROM THE WALLS OF A LATERAL VENTRICLE IN RAPIDLY PROGRESSING HYDROCEPHALUS. BERNARD S. EPSTEIN, Am. J. Roentgenol. **67**:929 (June) 1952.

Normal or moderate dilatation of the lateral cerebral ventricles usually shows these chambers as smooth-walled cavities. With rapidly advancing hydrocephalus, ribbing of the roofs of the lateral ventricles may be observed. This is due to stretching of the blood vessels up to the limit of their elasticity, after which the ventricular walls continue to recede between the blood vessels. A case is presented showing this difference in resistance of white matter and blood vessels to the strain of advancing dilatation.

HODGSON, Rochester, Minn.

HYDRANENCEPHALY. ELISABETH MOSER, Ann. paediat. **179**:193 (Oct.) 1952.

A case of hydranencephaly in a boy of 31 days is described. Both hemispheres of the brain, apart from insignificant rests of basal gyri, were replaced by a fluid-filled double bladder the wall of which consisted of the two soft meninges and a small layer of glia with abundant deposits of hemosiderin. Clinically there were gradually increasing hypertonus of the whole muscular system, eclamptic attacks, disturbance of sucking and swallowing, and low temperatures. There is generally very little known about the pathogenesis and etiology of hydranencephaly. It is probably due to some morbid process during the fetal period; it is most probable that the brain, which is already formed, is destroyed during the second half of intrauterine life. Certain circulatory disturbances may be responsible.

FROM THE AUTHOR'S SUMMARY.

THE NATURE OF POSTMENINGITIC SUBDURAL EFFUSIONS. GAYLE G. ARNOLD, J. Pediat. **40**:757 (June) 1952.

Arnold reports that as demonstrated by electrophoresis the protein in subdural effusions is blood protein. The yellow pigment present in subdural effusions is one pigment and is derived from heme. Subdural fluids that collect after purulent meningitis should therefore be classed as erythrochromatic and not xanthochromatic.

Arnold theorizes that leptomeningitis may damage the boundary membranes of the arachnoid villi. The altered permeability of these membranes may then allow the passage of blood or blood serum into the subdural space. If bacteremia is present at the time of the "leak," the effusion may be purulent.

MACDONALD, Pittsburgh.

LISTERIA MENINGITIS IN A PREMATURE INFANT. F. G. LINE, and F. G. APPLETON, J. Pediat. **41**:97 (July) 1952.

The authors report a case of a premature infant with meningitis due to Listeria monocytogenes. The diagnosis was confirmed at the age of 12 days. Successful treatment included a combination of chlortetracycline (aureomycin), chloramphenicol, and oxytetracycline (Terramycin).

MACDONALD, Pittsburgh.

MODE OF ACTION OF SODIUM DIPHENYLHYDANTOINATE (DILANTIN) IN EPILEPSY. ROBERT B. AIRD and LOUIS STRAIT, J. Pharmacol. & Exper. Therap. **103**:136 (Oct.) 1951.

Diphenylhydantoin (Dilantin) raised the convulsive threshold of white mice treated with convulsive doses of cocaine hydrochloride. Data showed that a 20% decrease in the cocaine convulsive dose lessened the convulsions by two-thirds.

In cats protected by diphenylhydantoin, the amount of cocaine entering the cortex was lessened by 23% and that in the cerebrospinal fluid showed a decrease of 20% while the concentration of cocaine in the blood remained the same. Comparing these results, it was thought that the lowering of the cocaine blood concentration by diphenylhydantoin might well account for the protective effect of this anticonvulsive agent.

Since diphenylhydantoin lowered the permeability of the blood-cerebrospinal fluid barrier as well as the blood-brain barrier, it would appear that the element common to both barriers, namely endothelium, was the component affected by the hydantoin, a result which is in agreement with previous supravital dye studies.

PILCHER, Cleveland.

INFLUENZAL MENINGITIS TREATED SUCCESSFULLY WITH POLYMIXIN B (AEROSPORIN). HARRY LEICHENGER and LELABELLE C. FREEMAN, Illinois M. J. **102**:205 (Sept.) 1952.

A case of acute purulent meningitis due to Hemophilus influenzae was treated successfully with polymixin B (aerosporin) after no response was obtained from adequate doses of combined sulfadiazine and penicillin; oxytetracycline (Terramycin), and combined streptomycin and sulfadiazine. The patient, who had been critically ill for 21 days, showed improvement after 3 days,

and was apparently well after 6 days of polymixin B therapy. Complete recovery was noted in 12 days. Physical examinations made 12 days and 3 weeks, respectively, after polymixin B therapy was begun, showed the child had no evidence of any complications or residual findings. Urinalyses, blood counts, and blood smears were also normal. In this case effective therapeutic doses of polymixin B resulted in no evidence of toxicity.

FROM THE AUTHORS' SUMMARY.

PARADOXICAL CEREBRAL EXCISION IN HEMISPASTICS: PRELIMINARY REPORT. HUNTER J. MACKAY, Northwest Med. **51**:403 (May) 1952.

In this preliminary report on a new radical treatment for hemispastics, the author reports four cases of hemicerebral excision. With little else to offer the severely handicapped hemispastic youngster with cerebral palsy incapacitated by psychomotor seizures, the author and his associates reasoned that any abnormally functioning cortex was increasing the difficulty and that removal of the abnormal tissue might give the remaining normal cells a better chance to function properly.

Therefore, from four children with known left-sided lesions the entire left temporal, frontal, parietal and occipital lobes were removed. To the amazement of all concerned, these children recovered and demonstrated obvious improvement in spasticity, had no hemianopsia, were not aphasic, and had a marked reduction in their psychomotor seizures. The author concludes that to date the treatment of youngsters with hemispastic cerebral palsy has not been nearly radical enough and that ablative surgery offers new hope for these children. DOCTER, Seattle.

SALMONELLA BREDENEY MENINGITIS: CASE REPORT OF A 19-DAY-OLD INFANT. HOWARD KANTOR, Pediatrics **9**:597 (May) 1952.

A case of Salmonella Bredeney meningitis with recovery in a 19-day-old infant is reported. This is the youngest infant with Salmonella meningitis known to recover. No cases of Salmonella Bredeney meningitis have been reported in the literature.

This infant was admitted with a 24-hour history of apathy and anorexia. Two hours before admission a temperature of 38.8 C. (101.8 F.) was noted, and the infant was then seen at the hospital. The birth history and previous neonatal course were uneventful. Positive physical findings on admission were a temperature of 101.8 F., grayish cyanosis, and bulging anterior fontanel. Further signs of meningeal irritation were absent. Lumbar puncture revealed a purulent cerebrospinal fluid. Culture of the cerebrospinal fluid and the blood were positive for Salmonella Bredeney. This finding was confirmed by Erich Seligman, at the New York Salmonella Center.

Treatment with multiple antibiotics and chemotherapy both parenterally and intrathecally produced rapid clinical improvement. Intrathecal administration of streptomycin was considered instrumental in sterilization of the spinal fluid by the third hospital day, and the favorable and prompt clinical response that ensued. An equally effective supportive whole blood transfusion may have aided this recovery. The use of chloramphenicol (chloromycetin) after discontinuance of all other therapy (for a total of 17 days) effected a complete recovery. No sequelae were noted at the end of a three-month observation period.

Attempts at discovering the carrier state of the infecting organism through careful examination of the family revealed no source of infection. FROM THE AUTHOR'S SUMMARY.

RESULTS OF RADIATION THERAPY IN VASCULAR ANOMALIES OF THE CENTRAL NERVOUS SYSTEM. G. KAPLAN, B. ROSWIT, and E. G. KRUEGER, Radiology **59**:555, 1952.

The authors report nine cases of vascular malformations of the central nervous system, in all of which the treatment was first surgical, followed by x-ray therapy. In five of the nine cases the lesion was an arteriovenous angioma of the brain. In four of these it was observed surgically; in the fifth the diagnosis was made by means of cerebral angiography, and the common cartoid artery was ligated before x-ray therapy was given. In the other four cases

the lesion was a varix of the spinal cord. Surgical treatment consisted of decompression in all cases except the one in which ligation of the common carotid artery was the only surgical procedure. In one other case the carotid artery was ligated after surgical decompression.

The x-ray therapy varied considerably from case to case, both in quantity and in quality of radiation administered. The depth dose varied from 700 to 2,400 r in the series of nine cases. The total time of treatment also was extremely variable from case to case. The authors feel that no beneficial results were obtained from their x-ray therapy and that radiation has no role in management of vascular anomalies of the central nervous system.

WEILAND, Grove City, Pa. [A. M. A. Arch. Neurol. & Psychiat.].

METHODS OF ASSESSING THERAPY IN CHOREA WITH SPECIAL REFERENCE TO THE USE OF ACTH. A. ST. J. DIXON and E. G. L. BYWATERS, Arch. Dis. Childhood **27**:161 (April) 1952.

Methods of assessing the effects of therapy on the severity and duration of chorea are presented. Corticotropin (ACTH) treatment has been followed by these methods in four patients. The doses used were as great as, or greater than, those which in the authors' hands previously had produced rapid improvement in other manifestations of the rheumatic state. Corticotropin in this dosage does not benefit Sydenham's chorea.

KELLY, Milwaukee.

SUBDURAL EFFUSIONS IN INFANCY: TWENTY-FOUR CASES. A. N. GUTHKELCH, Brit. M. J. **1**:233 (Jan. 31) 1953.

Guthkelch presents a study of 24 cases of subdural effusion in infancy; 18 cases were of subdural hematoma, 5 of complicated purulent meningitis, and 1 of thrombosis of the sagittal sinus. The commonest symptoms in cases of subdural hematoma, in their order of frequency, were convulsions, vomiting, and irritability. Guthkelch considers subdural tap the only diagnostic procedure of value. Treatment consists in daily subdural taps for 10 to 14 days, after which craniotomy may be performed. Guthkelch also performed subdural taps once or twice in the first postoperative week. Of 16 infants treated in this way, Guthkelch has reason to believe that 10, or possibly 11, "will grow up into normal children."

It is generally agreed that subdural effusions should be suspected in any infant with meningitis whose clinical progress is unsatisfactory after three days of treatment or in whom fever, vomiting, convulsions, or a tense fontanel persists. Guthkelch believes that with early diagnosis the results of treatment should approach those obtained in infantile subdural hematoma.

A case of subdural effusion complicating sagittal-sinus thrombosis is also presented. On the basis of this case, as well as a study of others, Guthkelch concludes that "cerebral thrombophlebitis, whether it occurs from extension of infection from purulent meningitis or from a focus elsewhere, may give rise to a subdural effusion, and that the likely mechanism is the giving way of the necrotic walls of veins crossing the subdural space."

ECHOLS, New Orleans [A. M. A. Arch. Neurol. & Psychiat.].

ABLATION OF ABNORMAL CORTEX IN CEREBRAL PALSY. W. PENFIELD, J. Neurol., Neurosurg. & Psychiat. **15**:73 (May) 1952.

Cerebral palsy may be defined, in a broad sense, as loss of function due to brain injury. Such injury may affect motor centers, producing spastic paralysis of an arm or leg, but it may also affect other areas of the brain and thus cripple other functions than those of arm and leg movements.

Penfield subscribes to the thesis that abnormal cortex incapable of useful service does in some cases exert a noxious influence upon the rest of the brain which might otherwise function normally.

In this paper he reviews operative procedures and results in patients with epilepsy, mental retardation, and spasticity. He concludes that patients who suffer from cerebral palsy may be

benefited by cortical excision in various ways. However, he states they must be very carefully studied and selected before such radical procedures are to be considered.

The possible benefits follow: 1. The patient who is subject to recurring cerebral seizures may be relieved of his attacks. 2. The patient who has a discharging lesion of the cortex and shows progressive mental retardation may be greatly improved by excision of the partially destroyed cortex, provided intellectual degradation has not gone too far. This applies particularly to children in the early stages of mental retardation and behavior abnormality. 3. Patients with severe hemiplegia from infancy may be freed from spasticity to a considerable extent by excision of the motor cortex.

In the experience of the author and his colleagues, complete hemispherectomy is rarely advisable. But subtotal hemispherectomy and the discriminating ablation of all nociferous cortex may bring great improvement to selected patients with cerebral palsy.

ALPERS, Philadelphia [A. M. A. Arch. Neurol. & Psychiat.].

CEREBRAL ANGIOGRAPHY: ITS VALUE IN THE DIAGNOSIS OF VARIOUS INTRACRANIAL AFFECTIONS. A. J. BELLER and E. PEYSER, Harefuah **43**:27 (Aug.) 1952.

Angiographic studies were performed in 80 cases over a period of three years—since 1950 by the percutaneous method alone. Angiography is most useful in the precise diagnosis of intracranial vascular lesions, such as aneurysm and vascular malformation. In cases of such lesions the clinical picture is often atypical, and diagnosis without laboratory aid is extremely difficult. In three of five cases of sphenoidal-fissure syndrome the lesion was an aneurysm; in the other two it was a tumor. The only method of differential diagnosis in these cases was the angiogram. The apparent size of the aneurysm on the angiogram does not always corrspond to its actual dimensions. Only part of the aneursym may be filled with dye because of the formation of cyst-like structures at the site of bleeding. Only extradural aneurysms reach a large size; subdural aneurysms within the subarachnoid space rupture early. The authors report two cases of aneurysms in the anterior communicating artery in which diagnosis could be made only by angiogram. They cite the case of an arteriovenous malformation of the cerebral cortex with a history of Jacksonian attacks in a man aged 30. The electroencephalogram showed a focus in the left frontotemporal region. The veins and the arteries filled at the same time, without a capillary phase. In another case, one of traumatic carotid sinus fistula, the carotid artery was enlarged. This is also true of other blood vessels of the brain. In a man aged 50 with a six-year history of Jacksonian attacks without loss of consciousness right hemiplegia appeared after a head injury four months before his admission to a hospital. The weakness of the right side and the aphasia improved. Angiography showed an occlusion of the left middle cerebral artery and enlargement of the ventricle on the same side, after pneumoencephalography. Though the clinical course suggested a tumor, angiography and air studies indicated the presence of vascular occlusion. In another case the clinical picture was that of vascular disease, but the lesion was a tumor pushing up the middle cerebral artery, with typical bowing of the anterior cerebral artery. The authors state that more recently they have been using angiography alone in the diagnosis of expanding lesions. Of 43 cases of tumor of the brain, in which angiography was done, the tumor was demonstrated by angiography alone in 50%.

N. SAVITSKY, New York [A. M. A. Arch. Neurol. & Psychiat.].

STRUMPELL'S DISEASE. G. ACETO, Minerva pediat. **4**:491 (June 30) 1952.

A case of familial spastic spasmodic tetraplegia of Strümpell-Lorrain in a 2-year-old boy is reported. Five children in this family had this same disease, but no history of a similar condition could be obtained in preceding generations of either parent.

HIGGINS, Boston.

PROGRESSIVE PARALYSIS OF CHILDHOOD. ROSARIO RUGGERI, Pediat. riv. d'igiene med. chir. infan. **59**:621, 1951.

The author describes five cases of juvenile progressive paralysis with onset at the ages of 7, 9, 10, 11, and 12 years, respectively. In all cases the disease was initially accompanied with lability of memory, remarkable psychic changes, and anisocoria with lowered pupillary reaction.

Only one patient presented dysartry and two spastic paraparesis. Epileptic-like manifestations accompanied with complete loss of the speech occurred in another patient. The author reports results obtained with malaria therapy and specific drugs. The importance of an early diagnosis in these cases is emphasized in relation to the possibility of obtaining successful therapeutic results only by timely beginning of therapy.

FROM THE AUTHOR'S SUMMARY.

SEVENTY-TWO CASES OF PNEUMOCOCCUS MENINGITIS IN THE INFANT, WITH SPECIAL REFERENCE TO COMBINED TREATMENT WITH PENICILLIN AND SULFONAMIDES. JULIO MENEGHELLO and CARMEN AGUILO, Rev. chilena pediat. **20**:455 (Nov.) 1949.

The authors report on 72 cases of pneumococcus meningitis seen at the Manuel Arriaran Hospital during the years 1945 through 1948. Pneumococcus meningitis constituted 62% of all the cases of meningitis seen during this period in infants. Of the 72 patients, 26 patients died before 40 hours of hospitalization; 3 patients did not receive the combined sulfonamide-penicillin treatment, and 43 received this kind of treatment for more than 40 hours. The total mortality was 62.5%, and the selected mortality, 37.3%, since of 43 infants who received the combined treatment for more than 40 hours 16 died and 27 recovered.

Of the 27 infants who survived, 8 were discharged from the hospital with significant neurological sequelae and 2 with papilledema that has not affected vision during the time these infants have been under control.

FROM THE AUTHORS' SUMMARY.

PROGNOSIS AND THERAPY AF PNEUMOCOCCIC MENINGITIS. N. URBAN and A. STECHERN, Ztschr. Kinderh. **70**:411, 1952.

An analysis of 33 cases of pneumococcic meningitis led to the conclusion that sulfonamide therapy and intramuscular and intrathecal injections of penicillin in large doses over a long period gave the best results. The authors do not agree with the statements in other publications that intrathecal penicillin may be harmful and is unnecessary. They feel that there is no danger if doses are carefully determined and the drug properly diluted. They insist upon early elimination of a causative focus (antrotomy) and feel that the addition of streptomycin and chlortetracycline (aureomycin) will further improve the therapeutic results.

It was the authors' experience that prognosis as to the ultimate outcome cannot be made immediately after cure of the meningitis, since one of their patients was released apparently normal and weeks later convulsions, hydrocephalus, and mental retardation developed.

GLASER, Jerusalem.

News and Comment

ANNOUNCEMENTS

Course in Practical Pediatric Hematology.—A course in practical pediatric hematology will be given on Sept. 15, 16, and 17, 1953, at The Children's Hospital in Philadelphia, 18th and Bainbridge Sts. The director is Dr. Irving J. Wolman, Associate Professor of Pediatrics and Director of Laboratories of The Children's Hospital. Dr. Wolman will be assisted by Dr. Neva M. Abelson, of the Philadelphia Serum Exchange, and Dr. Benjamin Dickstein, Dr. Paul G. Eglick, and others. Tuition is $60. It will run from 10 a. m. to 5 p. m. on the first two days and from 9 a. m. to 4 p. m. on the third day.

Standard for Audiology Center.—The Bureau for Handicapped Children of the New York City Department of Health is publishing in mimeograph form the "Recommended Standard for Audiology Center."

PERSONAL

A portrait of Dr. Tom Mitchell, Professor of Pediatrics of the University of Tennessee College of Medicine and Chief of Staff of the Le Bonheur Children's Hospital, was presented to the University of Tennessee June 11, 1953, in honor of his many years of service in the division of pediatrics. The portrait was hung in the conference room of the Le Bonheur Children's Hospital.

Books

Applicazioni della stratigrafia assiale trasversa in pediatria. By R. Bulgarelli, A. DeMaestri, G. Sansone, E. De Toni, C. Lombroso, L. Oliva, N. Macarini, P. Durand, and G. Corradi. Price, 2,000 lire. Pp. 350. Edizioni Minerva medica, Via Martiri della Liberta, 15, Torino, 1951.

This book contains a collection of articles appearing in the May and June 1951 numbers of *Minerva Pediatrica*; abstracts of these articles have appeared in the AMERICAN JOURNAL OF DISEASES OF CHILDREN. The authors are members of the radiology and clinical pediatric staffs of the University of Genoa.

A technique for stratigraphy has been worked out in the x-ray laboratory in which the x-rays are focused on a given horizontal plane of the body from an angle, the film and the patient both being rotated during the exposure. Thus pictures of various parts of the body can be obtained. There are presented some excellent illustrations from films which show horizontal x-ray views of various levels of the body trunk; they visualize pathology in congenital malformations of the heart and great vessels, of the anterior and posterior mediastinum and thymus, and of the pancreas, the bladder, and other abdominal organs. There are also illustrations of films taken by stratigraphy of the head during pneumoencephalography. The illustrations are accompanied by anatomical diagrams to explain the shadows seen.

The possibilities of stratigraphy are well outlined. The ultimate practical value of the procedure remains to be seen.

Les feuillets du pédiatre: Edition définitive. Germain Blechmann. Paper. Price, 1,950 francs. Pp. 388, with 17 illustrations. Gaston Doin & Cie, 8 place de l'Odéon, Paris, 6e, 1951.

This unique book consists of a series of short articles and lectures given by the author. They have been placed in order of feeding, newborn, diseases of children, and various problems of pediatric interest, so that it is in the form of a pediatric textbook, and the continuity has in no way been lost.

They are very informative and readable, and in skimming the book one continually stops and reads one of the very interesting discourses. Although the book is written in French, the illustrations and tables make it very interesting reading for the average physician. It is a charming little book.

Tesaurismosis en el niño. By Maria Luisa Saludún de Rodriguez, Euclides Peluffo, and Alejandro Volpe. Paper. Price, not given. Pp. 154, with 44 illustrations. Imprenta de Alfredo Frascoli, Belgrano 2563, Buenos Aires, 1950.

In this excellent monograph the authors have classified thesaurismosis into, first, the usual group of the hepatic, cardiac, and miscellaneous forms. In the second group they consider the lipoid disturbances, such as Hand-Schüller-Christian and Letterer-Siwe diseases and eosinophilic granuloma, and including the reticuloendothelial group of Gaucher and Niemann-Pick diseases and amaurotic family idiocy. The final member included in this group is calcinosis.

The book is very well written, and the thesis is given considerable authority by inclusion of case studies of examples of the various diseases mentioned. The illustrations, mostly photographs from the cases described, are very well chosen. There is also an excellent bibliography of all literature on this subject. This is as thorough a study of glycogen storage and allied metabolic disturbances as has been written, and, although in Spanish, is very readable. It should be read in detail by those interested in this subject.

The Audiology Clinic. By Dr. Moe Bergman. Price, $1. Pp. 107, with 18 figures and 1 table. AAS & Wahls Boktrykkeri, Oslo, Norway. Copies may be obtained by writing The Audiology Foundation, 1104 S. Wabash Ave., Chicago 5.

The material in this monograph is based upon the experience and knowledge acquired in the military and Veterans Administration auditory rehabilitation units for acoustically handicapped adults. The presentation will be of invaluable aid to planners of hearing rehabilitation centers in the United States and other countries. Included in the monograph are chapters on the necessary instructional program, designing and equipping the audiology clinic, personnel requirements, and audiology facilities for the rehabilitation of the acoustically handicapped in the United States. There are valuable appendices containing suggested sources and the approximate costs of equipment items and a selected bibliography.

Although this publication will have a limited appeal, it doubtless represents the most authoritative correlation to date of the various allied activities in the new science of audiology. It certainly can be studied with benefit by all those interested in the fields of otology, acoustics, and speech therapy.

Problemas del prematuro. By Jose Obes Polleri. Pp. 98, with 25 tables. No price given. Garcia Morales, Mercant Graficos Unidos S. A., Montevideo, Uruguay, 1950.

This monograph is based on studies resulting from the Problems of the Premature read at the Congreso Sudamericano de Pediatria in Buenos Aires in 1949 and 1950. It contains chapters on the definition of prematurity and statistics on the frequency, causes of mortality, and the initial crisis of the premature infant.

The subjects are dealt with in a complete fashion. Not only are the literature and statistics from the author's own locality thoroughly studied, but also those from other foreign countries. The chapter on statistics is of particular interest, as the mortality from different countries is split up into weights of the premature infants, day of death, sex, and other interesting subdivisions. The chapters on care of the premature infant are complete, and controversial subjects are fairly met. The conclusions are that much can be done to reduce the mortality of the premature infant by standards of care and hospital treatment.

Although written in Spanish, this book should be intensely interesting to anyone interested in this subject. The bibliography is excellent and covers the field of prematurity well.

Maternal Care and Mental Health. By John Bowley. Price, $2. Pp. 180. World Health Organization, Geneva, Switzerland, 1951. (May be obtained through Columbia University Press, 2960 Broadway, New York 27.)

This is a survey of the evidence of the effects of maternal separation upon infants and children made for the World Health Organization by a well-known English child psychiatrist. It covers the effects of all types of separation from complete deprivation in the institutionally reared child to the variable deprivation of the child with an emotionally disturbed mother. There is also an excellent discussion of the causes of maternal separation (illegitimacy, working mothers, hospitalization of mother or child, death of mother, etc.) and the efficacy or lack of it of various maternal substitutes (adoption, boarding homes, group care).

This is the best summary of the effects of maternal deprivation that this reviewer has seen. Every pediatrician should be aware of its devastating effects, particularly during the first two years of life. There are many implications applicable to the general care of children and especially to the hospitalized child. Pediatricians will also be interested in the fine summary of successful adoption practices.

There is only one relatively minor point which seems out of line with current thought in this country. The author apparently has no faith in the predictive value of infant testing under 18 months of age. While it is recognized that these tests are influenced by the experience and judgment of the examiner as well as the physical condition and previous situation of the child, there seems to be no doubt that they do have reliable, if not pinpoint, predictive value.

Genetics and Disease. By Tage Kemp. Price, 25 Danish kroner. Pp. 329, with 98 illustrations. Ejnar Munksgaards, Forlag, Nørregade 6, Copenhagen, Denmark, 1951.

The author of this book is professor of human genetics at the University of Copenhagen and director of the Danish Institute for Human Genetics. Since much sound and valuable work has been done in Denmark in the line of human genetics, this book should be of interest to the American physician as representative of current thought on this subject in Scandinavia.

The first part of the book deals with general principles of genetics. Chapters on consanguinity, twinning, and sex determination are of definite medical interest. The second part deals with the difficulties which the geneticist encounters in medical matters and with his attempts to overcome them. Part three deals with normal hereditary factors in man. The inheritance of morphologic, physiologic, and psychic traits is discussed. The longest chapter is devoted to the genetics of blood groups and incompatibilities. About one-third of the book is devoted to hereditary diseases. Most disorders are discussed rather briefly, which is understandable in a book of limited size. But it is regrettable that the reader interested in details can not find references to the articles from which the author derived his opinions. The last part of the book is entitled "Genetic Hygiene" and deals "with that part of eugenics which has the sole task of preventing disease." To physicians interested in this controversial matter it will be of value to become acquainted with the sound and well-balanced attitude of a leading Scandinavian geneticist toward this difficult problem.

Terapéutica clínica infantil. Edition 2. By Juan Bosch Marin and Luis Cardona Mateo. Price, 125 pesetas. Pp. 632. Gráficas González, Miguel Servet, Madrid, 1950.

The second edition of this book has been completely revised and brought up to date. It contains a description of the accepted therapy in all the various diseases of infancy and childhood. Excellent chapters are those on infant feeding, in which all of the standard infant feeding formulas are discussed with their methods of preparation, diseases of the newborn, diseases of the various systems, and a final chapter on the common skin diseases seen in pediatrics.

In all of these conditions the treatment is not only given in detail but a list is appended of the various forms and types of medication marketed by the various pharmaceutical companies; so that the reader will know just what may be obtained. All of these treatments are quite modern, and all are accepted forms of therapy.

Although written in Spanish, this book is very clear and easily read by anyone, and is a very interesting and valuable edition to the pediatric literature.

Preventive Medicine and Hygiene. Edition 7. By M. J. Rosenau, edited by K. F. Maxcy. Price, $14. Pp. 1,500, with 131 illustrations. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1951.

This seventh edition of Rosenau's well known "Preventive Medicine and Hygiene" is indicative of the drawing together of clinical medicine and public health. A large proportion of the clinician's patients come to him for preventive services and for advice about the maintenance of health. At the same time the health officer and his staff are correspondingly responsible for the organization of clinical services for those diseases and for those groups of the population requiring community endeavor.

This volume begins to bridge the ground between the clinical and the public health approach. It is written primarily for the health officer and his staff, but it contains a great deal which is of value to the clinician. Most of the chapters in the sections dealing with the prevention of communicable disease and with the maintenance of health are written by physicians with a clinical background. For example, the chapters on tuberculosis and on mental health have much material not found in the usual textbook of medicine which will be of value to both the clinician and the health officer. The chapters on the diseases carried by mosquitoes, lice, ticks, and other arthropods are particularly well done.

The shortcomings which can be found in the book are those which are common to all attempts to crowd a great deal of information into small space. In most instances this problem is handled by an excellent reference list. A notable exception is the section on whooping cough,

which is well done, but which carries no references more recent than 1933, in spite of the fact that the evidence on which the trend toward early immunization is based has been developed since that time. Again, the material on the mosquito-borne encephalitides is well presented from the clinician's point of view, yet in the section on Rocky Mountain Spotted Fever there is no comment to the effect that the introduction of antibiotics against this disease has greatly reduced the use of active immunization.

One should immediately add that this sort of minor fault is rare; and one should also say that the scope of the volume is so broad as to pose an almost impossible task for the reviewer. One would need to be a specialist in many fields, including nonmedical, although closely related, activities, to do justice to the volume. The sections on food sanitation, environmental medicine and industrial hygiene, sanitary control of water supplies, and sewage and refuse disposal are examples of related disciplines which appear to this reviewer to be well done.

Particular mention should be made of the chapters on statistical reasoning and the health of the population, which presents this material in a clear and simple manner which should be valuable to all physicians.

El Prematuro. By Jose Obes Polleri. Price, not given. Pp. 273, with 27 tables. Reprinted partially from the *Archivos de pediatriá del Uruguay*. Revised and amplified by Mead Johnson & Company. Garcia Morales,-Mercant S. A., Montevideo, Uruguay, 1952.

This is a very complete and up-to-date discussion of the premature infant. The subject matter is divided into five sections: conception and definition, statistical study, causes of prematurity, emergencies of the early period, and digestion and pathology. All of these are fully covered with deference to the various opinions that may exist on debatable questions. These problems are all documented with full references so that the reader can see both sides of the problem.

This is a very excellent book and, although written in Spanish, very readable. The bibliography is full and excellent, being as complete on the subject of prematurity as the reviewer has seen. This book should be read in full by those interested in the subject.

Endocrine Treatment in General Practice. Edited by Max A. Goldzieher, M.D., and Joseph W. Goldzieher, M.D. Price, $8. Pp. 474, with 19 illustrations. Springer Publishing Co., Inc., 44 East 23rd St., New York 10, 1953.

The authors deserve praise for the presentation of a comprehensive treatise dealing with the diagnosis and detailed therapy of endocrine disturbances. Rather than giving the classical disease patterns of the ductless glands with the usual anatomical, physiological and pathophysiological features of each, the authors have presented the essential diagnostic features and details of endocrine therapy in a new and helpful way. A portion of the text is devoted to disturbances of growth and age, and again to disturbances of food and mineral metabolism. In the latter section is a convenient enclosure with the new exchange system of foods worked out for ready application by the busy general practitioner.

The larger portion of the text is devoted to the disorders of each of the body-organ systems.

Very excellent chapters are those devoted to male infertility, disorders of menstrual function, female sterility, and the menopausal syndrome. The book is repetitious and lacks cohesiveness, which makes reading at times laborious. However, some merit may be found in these repetitions in that the general practitioner may have a cross index to his problem. In general, there is a conservative tone used by most of the authors in their approach to this rapidly expanding and at times controversial field.

However, in the reviewer's opinion, there are instances in which there is too much enthusiasm for the use of the pituitary and adrenal hormones, which leads to difficulties in the hands of an inexperienced practitioner.

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Meat occupies a prominent position in the weight reduction diets outlined in this American Heart Association booklet. This recommendation is in sharp contrast to the erroneous belief held in former years that meat is harmful in hypertension or cardiac disease. "There is no evidence that red meat or any other form of protein in moderation has any adverse influence on blood pressure."

The magic formula for reducing is simply "Eat less." Two types of diets are outlined. One "allows moderate amounts of meat and other proteins, small amounts of fat and moderate amounts of carbohydrates." The other is "high in protein with plenty of meat, eggs and cheese, moderate in fat and low in carbohydrates." Diet No. 1 provides 70 Gm. of protein, 60 Gm. of fat, and 120 Gm. of carbohydrate; caloric yield, 1,300. Diet No. 2 provides 100 Gm. of protein, 80 Gm. of fat, and 60 Gm. of carbohydrate; caloric yield, 1,360.

The inclusion of generous amounts of meat in these diets—12 to 16 ounces of cooked meat or two substantial servings each day in Diet No. 2—is a reflection of the important role meat plays in any weight reduction regimen. It is generously included because of its high content of protein of excellent biologic value and because lean meat contains unobjectionably small amounts of fat.

*Food For Your Heart, a Manual for Patient and Physician, Department of Nutrition, Harvard School of Public Health, Harvard University, The American Heart Association, Inc., New York, 1952. Copies available through local Heart Association.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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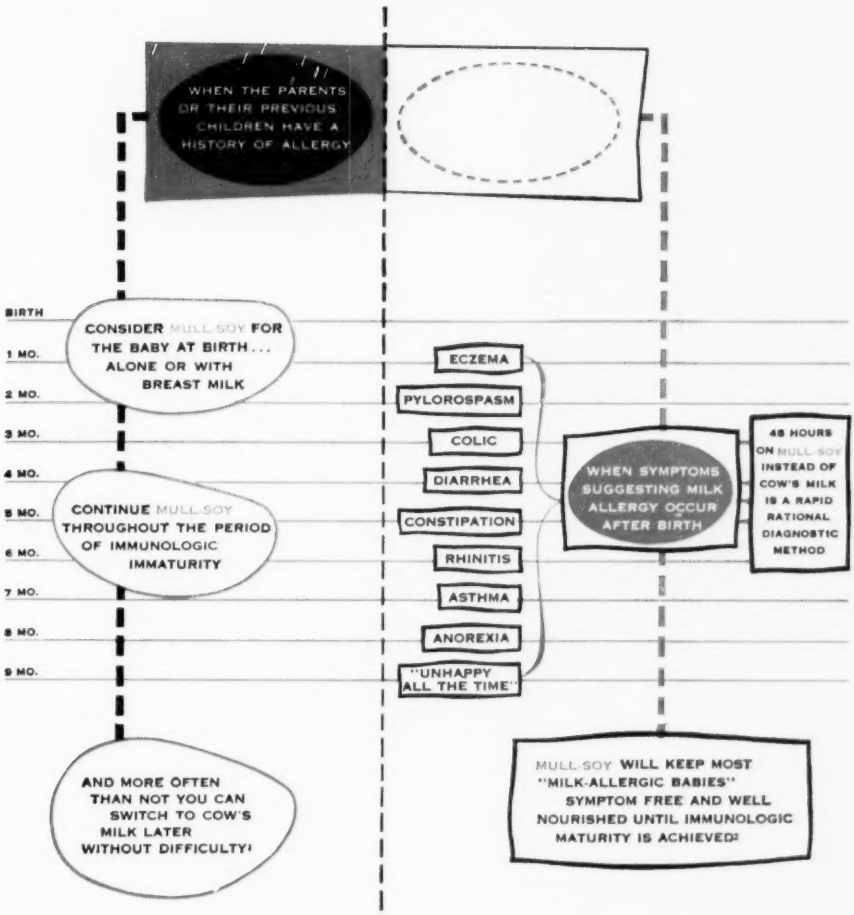
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1. Glaser, J., and Johnstone, D. E.: Ann. Allergy 10:433, 1952.
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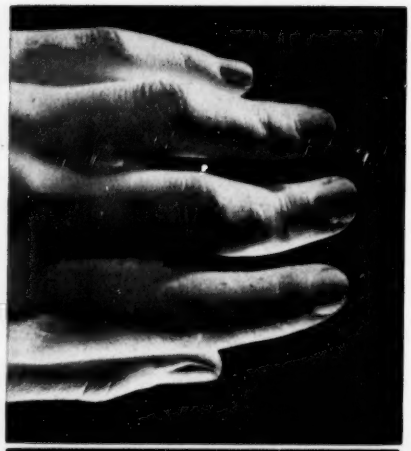

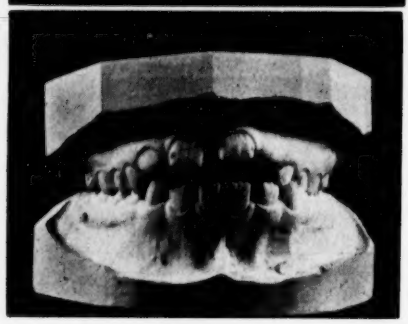

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REFERENCES:

* 1. Sulzberger, M.D., Wolf, J., "Dermatology," 1952, The Year Book Publishers, Chicago.
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5. Callaway, J. L., Crane, G. W., Jr., Current Therapy, 1952, W. B. Saunders Co., Philadelphia.

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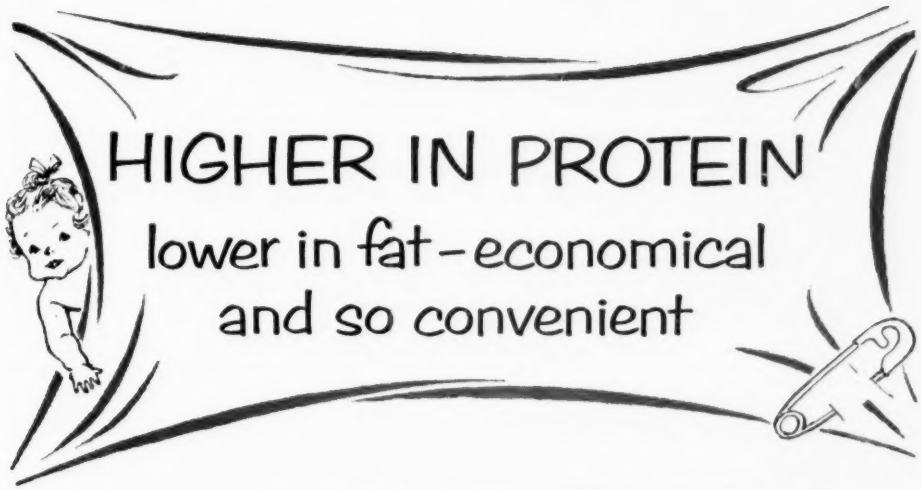

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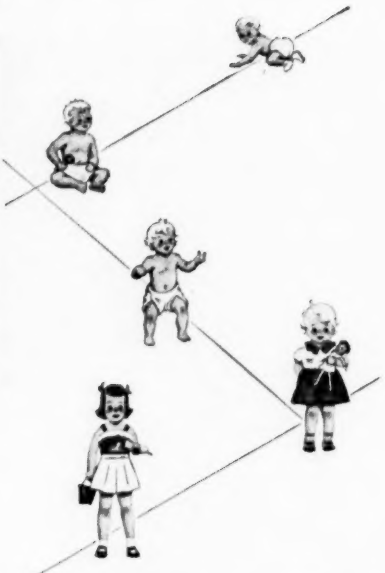

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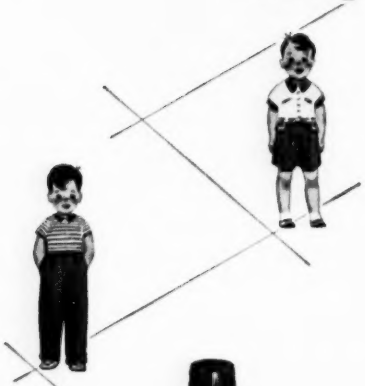

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Burgess, T. S.: *Jour. Med. Assn. Georgia*, 37:44, Feb., 1948.

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